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# RESULTS OF SPINAL PYRAMIDOTOMY IN THE TREATMENT OF THE PARKINSONIAN SYNDROME

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THE NEED for a method affording relief through surgical measures to patients suffering from severe parkinsonism can scarcely be questioned by anyone who has had to do with this unhappy group. The use of drugs of the belladonna series should, of course, always be tried, and if it is satisfactory surgical intervention need scarcely be considered; but failures are numerous, and, all in all, the medical profession has little reason to be complacent over the results so far obtained. It has been clearly shown by several surgeons that relief of tremor is possible following various procedures which destroy the pyramidal tract to a greater or less degree (Bucy,[1] Putnam,[2] Klemme,[3] Myers[4]), but it remains to be seen which of the operative methods yields the most satisfactory results in the long run.

From the Department of Neurology, Columbia University, College of Physicians and Surgeons; the Neurological Institute of New York, and the Cedars of Lebanon Hospital, Los Angeles.

1. Bucy, P. C., and Case, J. T.: Tremor: Physiologic Mechanism and Abolition by Surgical Means, Arch. Neurol. & Psychiat. **41**:721, 1939; Cortical Extirpation in the Treatment of Involuntary Movements, A. Research Nerv. & Ment. Dis., Proc. **21**:551, 1942; The Precentral Motor Cortex, Urbana, Ill., University of Illinois Press, 1944; Surgical Relief of Tremor at Rest, Ann. Surg. **122**:933, 1945.

2. (*a*) Putnam, T. J.: Treatment of Unilateral Paralysis Agitans by Section of the Lateral Pyramidal Tract, Arch. Neurol. & Psychiat. **44**:950 (Nov.) 1940; (*b*) The Operative Treatment of Diseases Characterized by Involuntary Movement (Tremor, Athetosis), A. Research Nerv. & Ment. Dis., Proc. **21**:666, 1942; (*c*) Alternating Tremor (Paralysis Agitans) and Athetosis: Recent Advances in Diagnosis and Treatment, New England J. Med. **222**:473, 1940.

3. Klemme, R. M.: Surgical Treatment of Dystonia, Paralysis Agitans and Athetosis, Arch. Neurol. & Psychiat. **44**:926 (Oct.) 1940; Surgical Treatment of Dystonia, A. Research Nerv. & Ment. Dis., Proc. **21**:596, 1942.

4. Myers, R.: The Modification of Alternating Tremors, Rigidity and Festination by Surgery of the Basal Ganglia, A. Research Nerv. & Ment. Dis., Proc. **21**:602, 1942; The Present Status of Surgical Procedures Directed Against the Extrapyramidal Diseases, New York State J. Med. **42**:535, 1942.

Aside from such practical considerations, many questions of great theoretic importance are also involved, for each of the surgical operations which has been proposed constitutes an interesting physiologic experiment.

### SCOPE OF THE PRESENT INVESTIGATION

The purpose of the present paper is to analyze a series of 22 cases of the parkinsonism syndrome which could be followed for a period of twelve months or more after operation. The total number of patients operated on is now over twice that number, but some cannot be reached and it is too early to draw dependable conclusions from the others. Most of the patients whose cases are included here were examined by one or the other of us in person, but in a few cases data furnished by other physicians were accepted. Preoperative and postoperative motion picture records were taken and used in the analysis whenever possible. Particular attention was paid to the influence of the operation on the tremor and on other manifestations of parkinsonism considered separately; also to the impairment of strength and motility at various intervals following operation. The general course of the disease process was recorded and, in particular, any increase in rigidity or spread of tremor to previously unaffected portions of the body. In cases with bilateral symptoms, any alteration in the condition of the side contralateral to the operation was given particular attention.

The technic of spinal pyramidotomy has already been described,[2a, b] and no important changes have been made in the operative procedure. A hemilaminectomy at the second cervical vertebra is to be preferred, and the lamina should be removed as far laterally as possible. Exposure is facilitated if the incision in the dura is curved, with the base of the flap at the level of the posterior roots, or even farther laterally. The landmarks are clear, and there is seldom difficulty in obtaining a field free of small pial vessels. If necessary, hemostasis may be assured by a touch of a cautery, heated only to a point sufficient to cause it to adhere to connective tissue.

This operation may easily be combined with Puussepp's operation, of section of posterior columns. Such a combined procedure was carried out in 5 cases, 4 of which are included in the present series. Its effect on rigidity was negligible. Surprisingly, disturbances of sensation were extremely slight. We hope to report more fully on them elsewhere.

The indications for spinal pyramidotomy will be discussed after presentation of the material. All the operations reported here were unilateral; the use of a combination of spinal pyramidotomy with homolateral cortical operation at a later stage and of bilateral spinal operations will be described in a later paper.

By the use of the technic described, the exposure is so good and the landmarks are so clear that there can be little question that the

procedure divides the lateral pyramidal tract and little else. A specimen was presented in the original paper to demonstrate this fact, but the present series do not permit any further proof of it, as there have been no deaths.

### CLINICAL DATA

Essential facts in the history and findings of possible importance in respect to the results of operation are presented in table 1. The age at onset of the first symptoms varied with the underlying disease process. A history suggestive of encephalitis was obtained in 6 cases, and in these the symptoms began in the second or third decade of life. In the majority of cases, no etiologic factors were apparent and the disorder was classified as "idiopathic." In this group, there was a gradual development of tremor and rigidity beginning in the fourth or fifth decade. In 2 cases, the sudden onset at the ages of 65 and 68 respectively and the presence of pronounced vascular changes led us to assume that the disease was arteriosclerotic in origin. For 2 patients, whose first symptoms began at the ages of 22 and 23 respectively, no history of encephalitis or other probable etiologic disorder could be elicited, nor was there any evidence of a corneal ring or disturbance of function of the liver. These 2 cases are provisionally considered as belonging to the "juvenile idiopathic" group.

### DEGREE OF INVOLVEMENT

The characteristic syndrome of regular alternating "parkinsonian" tremor and rigidity was seen in all cases. The term "rigidity" is used to characterize all akinetic phenomena: the loss of spontaneity, the slowness and inefficiency of active movements, the typical "waxy" resistance to passive movements and the loss of associated and synergistic innervation.[5] The regularity of the alternating tremor and the characteristic synchronous firing of motor units in the affected muscles were studied in slow motion pictures and by electromyography.

In 5 cases, only one side was involved, usually to a crippling extent, while the other was substantially normal. In 4 other cases, the tremor was unilateral but both sides were affected by rigidity. In 13 cases, tremor and rigidity were present bilaterally, but in 11 of these the symptoms were much severer on one side than on the other.

During the long course of the disease, all patients had undergone intensive treatment with various atropine and belladonna preparations, in all cases including one or more of the "Bulgarian" type. The interval between the onset of the first symptoms and the operation was never less than one year; in 13 cases it was less than two years; in 7, between twenty-six and forty-three months, and in 2 cases, fifty months or more.

5. Herz, E., and Putnam, T. J.: Motor Disorders in Nervous Diseases, New York, Kings Crown Press, 1946.

TABLE 1.—*Clinical Data Before and After Operation*

| Case | Sex | Age at Onset | Etiology | Degree of Involvement | Preoperative Duration, Months | Postoperative Result | | Interval to Last Operation, Months | Personal Follow-Up | Report from Physician | Final Result | | Course After Operation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Tremor | Motor Strength | | | | Tremor | Motor Power | |
| 1 | F | 14 | Postencephalitic | Bilateral rigidity; tremor on left | 24 | Absent | Complete paralysis | 19 | + | .. | None | Strength reduced; active movements possible | Static |
| 2 | M | 38 | Idiopathic | Unilateral (left) rigidity and tremor | 60 | Absent | Only weak movements of wrist and lower extremity possible | 53 | .. | + | Only slight when arm held in position | Reduction in arm 75%; in leg 50% | Static |
| 3 | F | 40 | Idiopathic | Bilateral rigidity; tremor on right | 72 | Improved 50% | Weakness, movements possible | 21 | .. | + | Severe bilateral tremor | Totally handicapped by severe rigidity | Progressive tremor on both sides |
| 4 | F | 65 | Arteriosclerotic | Bilateral rigidity; tremor greater on right | 60 | Absent | Complete paralysis | 18 | + | .. | Improved 80% | Painful contractures due to arthritis | Died of pneumonia |
| 5 | F | 48 | Idiopathic (heart disease) | Bilateral rigidity and tremor greater on right | 60 | Absent | Complete paralysis | 24 | + | .. | Slight return | Some return of strength in upper and paralysis of lower extremity | Died after bilateral frontal lobotomy |
| 6 | M | 14 | Postencephalitic | Bilateral rigidity; tremor on right | 144 | Absent | Complete paralysis | 14 | + | .. | Absent | Strength of arm improved | Died in mental disease institution after psychosis |
| 7 | F | 36 | Idiopathic | Bilateral rigidity; tremor greater on right | 84 | Absent | Slight impairment of strength; movements possible | 15 | + | .. | None; slight instability of active movements | Severely handicapped by bilateral rigidity | Progressive |
| 8 | M | 43 | Idiopathic | Unilateral (right) rigidity and tremor | 144 | Absent | Complete paralysis | 53 | .. | + | Improved only slightly; worse than after operation | Slight impairment of strength | Static; remained unilateral for 16 years |
| 9 | M | 14 | Postencephalitic | Bilateral rigidity and tremor; equal on 2 sides | 22 yrs. | Absent | Reduced | 18 | + | .. | Only slight when excited | Very slight reduction | Static |
| 10 | M | 44 | Idiopathic | Unilateral rigidity and tremor (left) | 72 | Absent | Definite weakness; movements possible | 19 | + | .. | As severe as before operation | Not impaired | Progression of tremor to other side |
| 11 | F | 68 | Arteriosclerotic | Rigidity and tremor greater on right | 2 | Absent | Considerable power in right hand | 26 | .. | + | Reduced 50% | Good | Died of coronary thrombosis |
| 12 | M | 23 | Undetermined | Unilateral (right) rigidity and tremor | 72 | Absent | Complete paralysis | 39 | + | .. | Absent | Slight reduction of strength | Static |
| 13 | M | 43 | Idiopathic | Bilateral rigidity; tremor greater on left | 120 | Absent (only 3 days) | All movements possible; only reduction of strength | 42 | .. | + | Equal; pronounced at two sides | General weakness | Progressive |
| 14 | F | 23 | Postencephalitic | Bilateral rigidity; tremor on left | 144 | Absent | Weak movements in shoulder, elbow and knee possible | 33 | + | .. | Improved; pronounced only when upset | No impairment | Static |
| 15 | M | 11 | Postencephalitic | Bilateral rigidity; tremor greater on right | 108 | Absent | Complete paralysis | 43 | + | .. | Absent; only slight tremor of thumb | Only severe rigidity; strength equal on 2 sides | Static |
| 16 | M | 46 | Idiopathic | Bilateral rigidity; tremor greater on left | 60 | Absent | Complete paralysis | 12 | .. | + | Minimal; definite improvement | Still paretic | Progressive; tremor greater on right |
| 17 | F | 44 | Idiopathic | Bilateral rigidity and tremor greater on right | 132 | Absent | Complete paralysis | 13 | + | .. | Absent at rest; present during movements | No paresis; severe impairment by rigidity | Progressive |
| 18 | M | 51 | Idiopathic | Bilateral rigidity and tremor greater on right | 72 | Absent | Complete paralysis | 15 | .. | + | "Worse than before operation" | Weakness | |
| 19 | M | 50 | Idiopathic | Unilateral (left) rigidity and tremor | 60 | Reduced | Weak movements possible | 15 | + | .. | No improvement | No reduction of strength | Slightly progressive |
| 20 | M | 45 | Idiopathic | Bilateral rigidity and tremor greater on right | 84 | Absent (for 10 days) | Only finger movements possible | 12 | .. | + | No improvement | Moderate diminution of motor strength | |
| 21 | M | 19 | Postencephalitic | Bilateral rigidity and tremor equal on 2 sides | 132 | Absent | Complete paralysis | 36 | .. | + | Absent | Somewhat diminished | Static |
| 22 | M | 22 | Not determined | Bilateral rigidity and tremor greater on right | 36 | Absent | Reduced 80% | 21 | .. | + | Bilateral tremor greater on left | Slightly reduced | Progressive |

All patients were severely handicapped in the use of the affected extremities, particularly by the intensity of the alternating tremor. Relief from this distressing symptom was urgently requested by each of them, even though the possibility of a loss of motor power was carefully explained to them. The majority of patients applying for surgical relief of their parkinsonism state were advised against having an operation, usually on the grounds that their chief disability consisted of rigidity rather than of tremor.

### RESULTS OF UNILATERAL PYRAMIDOTOMY

A study of this group of cases has amply confirmed the impression gained from the early operations of the series, that any improvement obtained affected preponderantly the alternating tremor. Rigidity was seldom noticeably decreased by section of the lateral pyramidal tract, and we have not been able to duplicate results in Fender's remark-

TABLE 2.—*Relation of Tremor and Impairment of Motor Strength at the Time of the Last Follow-Up Examination*

| Motor Strength | | Tremor | | |
|---|---|---|---|---|
| | | Abolished | Considerably Reduced | Not Influenced |
| Considerably reduced | 5 | 2 | 2 | 1 |
| Moderately reduced | 4 | 1 | 2 | 1 |
| Unimpaired | 13 | 4 | 4 | 5 |
| Total | 22 | 7 | 8 | 7 |

able case.[6] Additional section of the posterior columns performed in 5 patients has not seemed to have much effect on rigidity, as has already been pointed out.

*Immediate Results.*—Immediately after operation, the tremor was completely abolished in 20 patients out of the total of 22. In the remaining 2, its intensity was greatly decreased. Some impairment of motor power in the homolateral extremities was present in all patients. In 11 instances, complete paralysis was found directly after the operation, but in the remaining 11, there was merely impairment of motor power (table 1). In the latter group, active movements of some muscles were possible, sometimes with a strength estimated at 50 per cent of the preoperative strength. The proximal portions of the extremities were always more affected than the distal parts and the upper extremity more than the lower.

*Late Results.*—At the time of the last follow-up examination (table 2) visible tremor was still completely absent in 7 cases, with the excep-

6. Fender, F. M.: Personal communication to the authors.

tion that in 1 there was a negligible tremor of the thumb. The disappearance of tremor had persisted for periods varying from fourteen to fifty-three months, on an average for thirty-one months.

In 8 additional cases, the tremor at the time of the last examination was considerably improved as compared with the preoperative condition. There was either a decrease of more than 50 per cent of the tremor at rest, or tremor appeared only when the patient was under emotional tension or during voluntary motion or while striving to hold certain postures. This group was last reviewed at an interval of eighteen to fifty-three months after operation, on an average after twenty-five months. The reappearance of this slight degree of trembling was so gradual that patients could seldom give an exact date of its onset. In 1 case, traces of tremor had appeared ten days after the operation, but it was commoner for the onset to be delayed at least a month or two.

The operation was considered a failure in the remaining 7 cases. In 6 cases, the severity of tremor was at least as great at the time of the final examination as before the operation, and in 1 case the improvement was definitely less than 50 per cent. These patients had been followed for a period of twelve to forty-one months, on an average for twenty-two months. In 2 patients of this group the tremor had never been completely abolished by operation; in another 2 the tremor was absent for a few days only, and in the remaining patients the tremor reappeared not later than three months after operation.

Of particular interest, both practical and theoretic, is the course of the impairment of motor strength, which was present in all patients immediately after the section of the lateral pyramidal tract. At the time of the last follow-up examination (from twelve to fifty-three months, on an average twenty-six months after operation), the strength and active motility of the extremities affected by the pyramidotomy were still considerably reduced in only 5 patients out of 22. In these patients, although some feeble movements could be carried out, the strength of the extremities was insufficient for any real use. Of these 5 patients, the tremor had disappeared in 2, had been materially reduced in 2 others and persisted unabated in only 1.

In 4 patients out of the total 22, the strength of the extremities was still reduced at the time of the last follow-up examination but only to a moderate degree. These patients could perform all active movements. In 1 of these patients the tremor had disappeared; in 2 it had been considerably reduced, and in 1 patient it was uninfluenced by the operation.

In 13 patients the strength of the muscles on the affected side was not reduced or was reduced only to a negligible degree. In 4 of these, the tremor had disappeared; in 4 others it had been considerably reduced, and in 5 it was uninfluenced by the operation.

The evaluation of motor strength in this group of patients is not easy. It must be remembered that the akinetic symptoms, i. e., the loss of initiative, retardation of initiation of voluntary movement and the slowness of active motion, together with the increased resistance to passive movement produce a handicap in any performance test. In advanced cases, this impairment may be so severe that only a delicate evaluation of the muscle status can reveal the presence of additional loss of muscle strength attributable to the pyramidotomy.

Objective signs of lesions of the long descending motor tracts, in particular predominance of the deep tendon reflexes on the side of the pyramidotomy, were recorded in 12 cases and were reported to be absent in 2 cases. In 8 cases the neurologic data were incomplete in the reports available at the time of the last follow-up examination. In 7 cases, pathologic toe responses could be elicited in the lower extremities, but in only 1 case was the Hoffmann reflex observed. In 5 cases, disturbances in perception of pain and temperature were found on the side contralateral to the pyramidotomy, the result of course of a slight injury to the spinothalamic tract by the section. The occasional occurrence of this complication is an indication of the completeness of the operation.

There were no fatalities attributable to operation in this series. Four of the patients had died at the time of the last inquiry: 1 patient of pneumonia nineteen months after the operation, 1 of coronary thrombosis twenty-four months after operation, and 1 of unspecified causes in a mental disease institution, four years and seven months after operation. In 1 patient, bilateral frontal lobotomy was performed for the relief of a severe depressive state; she died a few days later, of arteriosclerotic heart disease, two years after the pyramidotomy. Unfortunately, no postmortem examinations could be obtained on any of these patients.

## COMMENT

This series of 22 cases could be followed for a considerably longer period after operation than was possible in the series of 6 cases reported when the operation of section of the lateral pyramidal tract was first suggested in 1940.[2a] The larger series and longer duration of observation appear to place the indications for operation on a firmer basis. In the first publication [2a] it was stated that "from the practical therapeutic point of view, it appears justifiable to conclude that operative treatment offers considerable hope of relief from severe unilateral tremor." The cases presented here permit more definite and detailed conclusions, in our opinion. In a group of 22 patients with severe, disabling parkinsonian tremor, two thirds showed a satisfactory improvement which lasted for at least a year. One third of the patients experienced

complete relief; in an additional third of the patients the tremor was markedly reduced, and only one third had results that can be considered failures.

It cannot be too often repeated that these generally favorable results relate to improvement of the tremor only. Neither section of the pyramidal tract nor any of the cortical extirpations which have been recommended are to be considered a treatment of parkinsonism; they are treatments only of tremor. The rigidity is seldom affected and the progress of the underlying disease is not checked. A complete and distinct understanding should always be reached with the patient and his family on this score; but in properly selected cases the prospects for improvement of function and increase of comfort may easily outweigh the disadvantages of the operation. If severe rigidity is present, improvement of function can scarcely be expected, but the patient may be rendered much more comfortable. The likelihood that the patient's condition will be made substantially worse in the long run as a result of this operation is extremely small. In this respect, it has a great advantage over the cortical operations, which often lead to disastrous results and at best usually produce a more serious disturbance of function than does the operation under discussion.

The danger to muscular power and control from this operation (and also from those at a cortical level) must be considered by both the surgeon and the patient. Both should realize that there is a risk of about 1 in 3 that the strength of the extremities involved will be substantially decreased even after the immediate postoperative period. If the tremor is in itself incapacitating, the exchange is usually for the better; but in other cases the possibility of further disability must be weighed against the probability of relief from tremor.

There appears to be no clear correlation between the age of the patient, the type of the disease or the postoperative relief from tremor and the incidence of paralysis after operation. There were 13 cases in this series in which there was no evidence of impairment of strength at the end of the period of observation. In 8 of these cases, there was satisfactory relief of tremor; in 5, little or no relief. Of the 9 cases in which there was considerable reduction of strength and control of the affected extremities, there was a satisfactory relief of tremor in 7 and unsatisfactory relief in 2.

A comparable study of the results of the cortical operation (resection of the premotor area) in parkinsonism has not as yet been published. The available observations (Bucy,[1] Klemme,[3] Putnam[2]) give definite evidence that the cortical approach may also yield good results in the improvement of tremor. Klemme's last report on 200 operations unfortunately lacks details about the preoperative clinical picture, the time of observation after the operation and the final result.

When the high mortality rate of 17 per cent in Klemme's series of operations is compared with the absence of mortality in our series of spinal operations, a large advantage would seem to lie with the latter. Furthermore, epileptic manifestations (Bucy, Putnam) seem to be a quite frequent manifestation after cortical resection. Finally, although complete analyses of results of the cortical operation are not available, we have personally seen and learned of many cases, especially those in which substantial amounts of cortex have been resected, in which severe and permanent paralyses and aphasias have occurred. The cortical operations appear, therefore, to be more dangerous in every way than the spinal pyramidotomies.

Although the final comparison between the cortical and spinal operation has to be postponed, two considerations are clear. The spinal pyramidotomy affects upper and lower extremities of one side. Cortical resection may be limited to one arm area. In solitary tremor of one upper extremity the cortical operation might, therefore, be preferred in order to prevent reduction of power in the lower extremity as a possible after-effect of the operation. Further, the cortical approach offers the opportunity of ascertaining approximately what result can be expected before the extirpation is actually carried out.[2b]

## SUMMARY

The results of spinal pyramidotomy were evaluated in 22 cases of the parkinsonian syndrome which could be followed for more than twelve months after the operation. The condition immediately after the operation and at the time of the last follow-up examination is described.

Of the various manifestations of the parkinsonian syndrome, only the alternating tremor could be favorably influenced. In one third of the cases there was complete disappearance of tremor; in an additional third the tremor was remarkably reduced, and in the last third the results were considered failures.

Reduction of motor strength, present in all cases immediately after the operation, subsided in the majority of cases but was still demonstrable to a smaller or larger degree in some cases.

This surgical procedure can be considered not a specific treatment of parkinsonism but a symptomatic treatment for tremor. Patients have to be selected carefully. The operation can be recommended without restriction to patients with severe distressing alternating tremor if akinetic symptoms and rigidity are not pronounced. In advanced conditions with disabling rigidity and severe tremor the usefulness of the extremities may not be improved by the operation, but the patient usually feels more comfortable after relief from the tremor, even though no more active.

The possibility of the persistence of reduction of motor strength after the operation has to be considered with this operation, as well as other operations for the relief of tremor, but the average disability appears to be less following spinal than following cortical and subcortical operations; there is no danger of convulsions, and there is a substantial difference in mortality in favor of pyramidotomy.

In the present series, the results of unilateral operations are presented. We have also had favorable experiences with the use of a unilateral pyramidotomy combined with a homolateral cortical operation, as reported by Scott,[7] and also with bilateral pyramidotomies, as first reported by Pimenta.[8] Our experiences have been too few and the time interval has been too short to permit definite conclusions concerning the results, beyond the fact that both types of operation are feasible, are not particularly dangerous and promise good results. Ebin's[9] proposal to sever the direct as well as the indirect corticospinal fibers also appears to have merit.

7. Scott, M.: Cerebral and Spinal Operations in a Case of Severe Postencephalitic Tremor, Arch. Neurol. & Psychiat. **51**:108 (Jan.) 1944.

8. Pimenta, W.: Personal communication to the authors.

9. Ebin, J.: Unpublished data.

# EXPERIMENTAL DEMYELINATION BY MEANS OF ENZYMES, ESPECIALLY THE ALPHA TOXIN OF CLOSTRIDIUM WELCHII

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DEMYELINATING diseases still constitute one of the major problems of neurology, and the lack of knowledge concerning their etiology is a constant handicap to rational therapy. The various manifestations of myelin degradation, as observed in the different demyelinating diseases, have been explained by divers causes: mechanical, chemical, infectious, immunologic and hereditary. The variety of mechanisms underlying the breakdown of myelin apparently is so great that one wonders with Hurst [1] whether demyelination is not a "type of response" of the nervous system to noxious stimuli of multiple causation. On the other hand, it may be that "demyelination" itself is not always precisely the same thing. The order of events and the extent of degradation may not always be identical in the demyelinating process, and the implications of these variations may be significant.

It was shown in 1931 [2] that experimental venous thrombosis might act as a contributory cause of demyelination. Since then a great deal of debate has centered about the importance of this observation, particularly with regard to multiple sclerosis. Regardless of whether the necrosis resulting from venous thrombosis is complete or incomplete, the myelin breakdown seems to be conventional in type, resulting in fatty degeneration and phagocytosis by macrophages.

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From the Departments of Neuropathology of the Harvard Medical School and the Massachusetts General Hospital and from the Medical Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University, located at the Massachusetts General Hospital.

1. Hurst, E. W.: A Review of Some Recent Observations on Demyelination, Brain **67**:103, 1944.

2. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931.

The observation that in chronic, intermittent, sublethal anoxic anoxia a form of demyelination may be produced which differs somewhat from the conventional breakdown of myelin has already been reported by one of us (L. R. M.).[3] Under these anoxic conditions it was found that in a Weigert or Weil stain for the myelin sheath there was sometimes macroscopic blanching of the white matter in pyroxylin preparations. Lesions of the myelin were equally conspicuous with Spielmeyer's stain in frozen sections. However, when fat stains were made, either sudan III (C. I. 248) or oil red O (C. I. 73), there was often no fat to be seen, and when these gelatin-mounted frozen sections were examined with polarized light the myelin sheaths were found to be anisotropic. In other words, some of the myelin had broken down part way into, or in a manner not including the production of, neutral fat or fatty acid. A similar observation had already been made by Hurst,[4] and before him by Ferraro,[5] on the brains of animals that had been exposed to chronic poisoning by potassium cyanide. One set of lesions was made by anoxic anoxia; the other set, by histotoxic anoxia. Since cyanide is well known as an inhibitor of respiratory enzymes,[6] the question arises whether enzyme systems are involved in producing the lesions of anoxic anoxia as well, and whether various enzyme system reactions in the brain may produce demyelination in different ways.

The myelin sheath is a complex structure, and "myelin" itself is not a living substance. While its breakdown by saponin, sodium taurocholate and other tissue destroyers may not be clearly understood, there are other approaches to the study of its degradation that are precise and specific. The lecithin, cephalin, sphingomyelin and other substances that make up its components present various avenues of attack by enzymes. The presence in the nervous system of any one, or any combination, of appropriate enzymes or enzyme inhibitors might affect the myelin sheath, and, depending on the specificity of an enzyme for its substrate, the myelin sheath might be variously modified. It is with this idea in mind that the work at hand is presented.

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3. Morrison, L. R.: Histopathologic Effect of Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **55**:1 (Jan.) 1946.

4. Hurst, E. W.: Experimental Demyelination of the Central Nervous System: III. Poisoning with Potassium Cyanide, Sodium Azide, Australian J. Exper. Biol. & M. Sc. **20**:297, 1942.

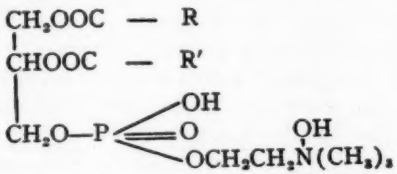
5. Ferraro, A.: Experimental Toxic Encephalomyelopathy: Diffuse Sclerosis Following Subcutaneous Injection of Potassium Cyanide, Psychiatric Quart. **7**:267, 1933.

6. Wyndham, R. A.: Experimental Demyelination of the Central Nervous System: II. Respiratory Enzyme Systems of the Brain in Poisoning with Cyanide and with Azide, Australian J. Exper. Biol. & M. Sc. **19**:243, 1941.

It has been well known since the work of Flexner and Noguchi,[7] and the more recent investigation of Weil,[8] that cobra venom contains a lecithinase which exerts a myelolytic effect on the nervous system. Frazer and associates [9] have recently pointed out that Clostridium welchii (clostridium perfringens) (type A) toxin may produce experimental demyelination in animals. The present experiments, in progress at that time, add evidence to the results of the in vitro experiment of these authors, in which they reported that distortion of the myelin sheaths and swelling of the axis-cylinders of an isolated sciatic nerve were found as a result of its incubation in Cl. welchii toxin.

## THEORETIC CONSIDERATIONS

If alpha lecithin is considered as the phospholipid of the myelin sheath to which most attention is directed in the present investigation, its structure may be expressed by the formula:



Any one or any combination of the three side arms—the saturated fatty acid (R), the unsaturated fatty acid (R′) or the choline ester of phosphoric acid—may be split off by action of appropriate enzymes. Finally, the choline alone may be split off.[10]

While it is true that both cobra venom and Cl. welchii alpha toxin contain lecithinase, these lecithinases are not identical. In cobra venom the enzyme splits off the unsaturated fatty acid from the middle arm of lecithin, leaving lysolecithin bound to the otherwise intact myelin sheath. In the case of the Cl. welchii alpha toxin the enzyme splits off the phosphorylcholine radical from the alpha arm, leaving fatty acids and glycerol bound.

In order to bring out these reactions histologically, two procedures are necessary: use of, first, a stain for normal myelin that will reveal the

7. Flexner, S., and Noguchi, H.: Snake Venom in Relation to Haemolysis, Bacteriolysis, and Toxicity, J. Exper. Med. **6**:279, 1902.

8. Weil, A.: The Effect of Hemolytic Toxins on Nervous Tissue, Arch. Path. **9**:828 (April) 1930.

9. Frazer, A. C.; Elkes, J. J.; Sammons, H. G.; Govan, A. D. T., and Cooke, W. T.: Effect of Cl. Welchii Type A Toxin on Body Tissues and Fluids, Lancet **1**:457, 1945.

10. Hanahan, D. J., and Chaikoff, I. L.: A New Phospholipide-Splitting Enzyme Specific for the Ester Linkage Between the Nitrogenous Base and the Phosphoric Acid Grouping, J. Biol. Chem. **169**:699, 1947.

damage to the myelin sheaths by the absence of staining, and, second, a histologic method for making visible the products split off by the lecithinase. The Weigert, Weil or Spielmeyer stain suffices for the first step.

For the second step two different procedures are necessary, since the cobra venom splits off a fatty acid, while the Cl. welchii alpha toxin splits off choline phosphate, the choline ester of phosphoric acid. The osmic acid after mordanting, or the sudan stains, reveal the fatty acids, especially when they are mixed with cholesterol, but none of the ordinary stains can be used to make choline phosphate visible. However, by a reversal of the technic of Gömöri,[11] the choline phosphate can be stained. The reaction in the present case is as follows: The substrate, namely lecithin, is intracellular, and an enzyme is added from outside which splits this intracellular substrate, with the liberation of an organic phosphate ester, choline phosphate. Therefore the Gömöri substrate is omitted, and for fixation an alcoholic solution of calcium nitrate is applied directly after incubation. Since calcium phosphorylcholine is rather insoluble under these conditions, it will precipitate in situ. It is not certain whether the eventually stained calcium precipitate is actually mostly choline phosphate or to a larger extent inorganic phosphate, which might be liberated through tissue phosphatase after preliminary liberation of the choline phosphate by the clostridium toxin. However this may be, the main point is that the staining procedure has given a means of showing and localizing the action of Cl. welchii toxin in the tissue preparation.

## MATERIALS AND METHODS

The investigation was divided into two principal types of experiments, in vitro and in vivo. In either type the object was to attempt to produce demyelination of the central nervous system of laboratory animals by the action of lecithinase on the myelin sheath.

*In Vitro Methods.*—Two technics were employed in the in vitro studies: the block technic, developed by Weil,[8] and the frozen section technic. Rabbit spinal cord, and less often brain, and mouse brain were the tissues most frequently used. The rabbits were quickly killed by the intravenous injection of air; the mice were rapidly exsanguinated, and the spinal cord or brain was promptly removed. In the block technic, slices of fresh, unfixed cord 3 to 5 mm. thick were placed in small (10 cc.) Petri dishes with the appropriate enzyme and incubated at 37.5 C. In the frozen section technic, similar-sized blocks of fresh, unfixed cord or brain were rapidly frozen in solid carbon dioxide to the metal disks of a Minot rotary microtome. Sections were cut at 24 microns in a cold chamber, according to the technic of Linderstrøm-Lang and Mogensen.[12] The frozen sections were either mounted on glass slides or received free in the enzyme solution and then incubated in the enzyme at 37.5 C.

11. Gömöri, G.: Microtechnical Demonstration of Phosphatase in Tissue Sections, Proc. Soc. Exper. Biol. & Med. **42**:23, 1939.

12. Linderstrøm-Lang, K., and Mogensen, K. R.: Studies on Enzymatic Histochemistry: Histological Control of Histochemical Investigations, Compt. rend. d. trav. du lab. Carlsberg, série chim. **23**:27, 1938.

Macfarlane and Knight [13] have demonstrated that the alpha toxin of Cl. welchii, type A, is probably identical with an enzyme capable of hydrolyzing lecithin. We used this lecithinase, as contained in Cl. welchii filtrates,[14] in most of the experiments; but for purposes of comparison a cobra venom lecithinase [15] was employed. Also, to a lesser extent, we have tried rattlesnake venom [16] and Bothrops jararaca venom.[17] The venoms were used chiefly in isotonic sodium chloride solution U. S. P. The Cl. welchii filtrate was sometimes used in a borate buffer $p_H$ 7.9 with free calcium ions added, but was most effective when dialyzed overnight at 2 C. against water or 1 per cent sodium chloride solution to remove the glycerin, and used in an aqueous solution, in the presence of calcium ions without any buffer. The presence of glycerin in the filtrates made it difficult to obtain reproducible results in the in vitro experiments.

In all cases appropriate controls were run; these consisted of the substrate and buffer without the enzyme, or, in the case of the toxic filtrate of Cl. welchii, the usual test solution with the addition of antitoxin in sufficient amounts. A suitable enzyme mixture was as follows:

| Test | Parts |
|---|---|
| Cl. welchii toxic filtrate | 8 |
| Calcium chloride, 0.02 M | 1 |
| Distilled water | 1 |
| **Control** | |
| Cl. welchii toxic filtrate | 8 |
| Calcium chloride, 0.02 M | 1 |
| Antitoxin [18] | 1 |

These various preparations, both tests and controls, were incubated in parallel pairs simultaneously at 37.5 C. for varying lengths of time between two and twenty-four hours. In most instances, immediately after incubation, the tissue, whether blocks or sections, was fixed in 10 per cent solution of formaldehyde

13. Macfarlane, M. G., and Knight, B. C. J. G.: Biochemistry of Bacterial Toxins: Lecithinase Activity of Cl. Welchii Toxins, Biochem. J. **35**:884, 1941.

14. We are indebted to Prof. Milan A. Logan for generous supplies of glycerinated Cl. welchii (type A) filtrates. Different batches of glycerinated (30 per cent glycerin) toxic filtrates have assayed from 500 to 1,700 mouse subcutaneous minimal lethal doses ($LD_{50}$) per cubic centimeter. These preparations were made by dialyzing sterile filtrates from Cl. welchii, type A, strain BP6K, against glycerin for eighteen hours at 2 C. The filtrate most used was found by Logan (personal communication) to contain chiefly alpha toxin, a small amount of theta toxin, (accounting for less than 5 of 1,000 minimal lethal doses) and 100 to 200 viscosity-reducing units and 2,000 to 6,000 mucin clot–prevention units of hyaluronidase activity per cubic centimeter. In referring to this preparation, we have used the term "filtrate" rather than "toxin," since there is evidence of the presence of three toxins, even though the alpha toxin, or lecithinase, is the principal component. Similar filtrates have more lately been obtained through the courtesy of Dr. I. S. Danielson, Lederle Laboratories.

15. Obtained through the courtesy of Hynson, Westcott & Dunning, Inc., Baltimore 1.

16. Supplied by Sharp & Dohme, Inc.

17. Obtained through Dr. Fritz Lipmann.

18. Antitoxin (polyvalent, Lederle) was present in one hundred fold excess over the toxin present.

U. S. P. (1:4). After fixation the frozen sections were stained by Spielmeyer's method for myelin sheath or by the oil red O method for fat. Some blocks, after fixation, were dehydrated and embedded in pyroxylin. Cut sections were then stained by Weil's method for myelin sheath. In an attempt to elucidate the alterations in myelin, other stains, such as the Marchi or Fischler stain, nile blue sulfate and sudan black B, were occasionally used.

In addition, as previously mentioned, Gömöri's technic [11] for the demonstration of phosphatase was adapted to the present investigation in the following way: In Gömöri's original technic, as well as in its modification by Wolf, Kabat and Newman,[19] the enzyme is present in situ in the tissue, and the substrate is added in the form of sodium-2-glycerophosphate or some other suitable phosphate ester. During incubation, phosphate ions are then split off at the site of reaction. In the present work, the enzyme, in the form of the lecithinase of Cl. welchii toxin, is added to a block of fresh spinal cord of rabbit, the lecithin of the myelin of which is the substrate, and incubated. On the assumption that this lecithinase liberates phosphorylcholine from lecithin [20] and that the liberated choline phosphate can be trapped at the spot by precipitation of an insoluble salt, the tissue is further incubated a short time, an hour or so, in a solution of 2 per cent calcium nitrate in 50 per cent alcohol. The tissue slices should be carefully handled to avoid unnecessary agitation, lest the calcium phosphate ester be washed out. The tissue is then fixed in 95 per cent alcohol, embedded in pyroxylin and sectioned. The sections are then placed for an hour in a solution of 2 per cent cobalt nitrate in 50 per cent alcohol, after being thoroughly washed in five or six changes of 50 per cent alcohol; they are then transferred for a few minutes to dilute ammonium sulfide, washed in alcohol, dehydrated and mounted. They may be counterstained with eosin if desired.

*In Vivo Methods.*—Dogs, rabbits and mice were used. A few injections of Cl. welchii filtrate were made intracerebrally, but in order to avoid direct trauma to the brain intravenous injections were usually performed. Most of the intravenous injections were given in a 10 cc. volume by syringe, but sometimes the filtrate was diluted to a volume of 100 cc. with sodium chloride solution and given by continuous drip method.

Certain animals were anesthetized by intravenous injection of pentobarbital sodium (30 mg. per kilogram of body weight); then the respiration and blood pressure were recorded by means of a kymograph. The cardiac output, hemoglobin content and hematocrit readings were also followed. There was progressive intravascular hemolysis, with a fall in cardiac output to shock levels and death.[21] Postmortem examination revealed congestion and edema of the lungs, liver, kidneys and small intestine. Only 1 dog survived the effects of the toxin. This dog was par-

19. Wolf, A.; Kabat, E. A., and Newman, W.: Histochemical Studies on Tissue Enzymes: III. A Study of the Distribution of Acid Phosphatases, with Special Reference to the Nervous System, Am. J. Path. **19**:423, 1943.

20. It has been stated (Zamecnik, P. C.; Brewster, L. E., and Lipmann, F.: J. Exper. Med. **85**:381, 1947) that the lecithinase of Cl. welchii has no effect on phospholipids other than lecithin. Our attention, however, has recently been called to the finding of Macfarlane (Biochem. J. [Proc.] **36**:3, 1942) that sphingomyelin is likewise split, although at a very slow rate. Repetition of our experiments on this point (unpublished data) with incubation overnight, rather than for a few hours, confirms Macfarlane's finding.

21. Zamecnik, P. C.; Nathanson, I. T., and Aub, J. C.: Physiologic Action of Clostridium Welchii (Type A) Toxins in Dogs, J. Clin. Investigation **26**:394, 1947.

tially protected from the hemolytic effect of the toxin by means of injections of a lecithin-containing lipid preparation.[22] Another dog had a violent fit, beginning one minute after administration of the toxin by syringe. This extraordinary event consisted of a sudden burst of hyperkinetic activity—unrestrained twisting of the body, rolling over and over, rapid snapping of the jaws and squealing—lasting about one minute. After this, the dog lay limp and panting in a corner. He began to have bloody defecations thirty minutes later, and then epistaxis. One hour from the time of injection he was dead. No neurologic abnormalities were observed in the other animals.

In order to see whether a longer survival time, together with more frequent exposure of the animal to the toxin, might have a severer effect on the central nervous system, 2 dogs were given repeated small doses at daily intervals. One of them received six injections each of Cl. welchii filtrate and Clostridium oedematiens toxin, ranging from 6 to 20 minimal lethal doses per kilogram of body weight, and died thirteen and one-half days after the first injection. The other was given injections six days a week for five and one-half weeks of doses of Cl. welchii filtrate which began with 6 minimal lethal doses per kilogram and worked up to 12 minimal lethal doses for the last fifteen injections.

Shortly after the death of an animal the brain was removed and placed *in toto* in dilute solution of formaldehyde U. S. P. After a day or two the brain was cut into blocks and then placed in fresh solution of formaldehyde until it was completely fixed. Then most of the blocks were embedded in pyroxylin, but some were used for frozen sections. Various stains were made, but in the present study Weil's stain for myelin and oil red O for fat were the principal stains employed.

Formaldehye-fixed preparations of the brains of 5 dogs that had received no Cl. welchii toxin were used as controls.

Various mice were also given the toxic filtrate of Cl. welchii. Some received repeated intravenous injections, and some were protected by hog liver lipids. Their brains were examined in preparations stained for myelin, as were the brains of normal controls.

### OBSERVATIONS DURING IN VITRO EXPERIMENTS

*Cl. Welchii Filtrate.*—Sections: After fixation in formaldehyde and staining by Spielmeyer's method, striking differences were observed between the test and the control sections, as can be seen in figure 1. While the control preparation appeared as a section of normal spinal cord, the test preparation presented widespread and extensive demyelination. On examination with the low power lens, all regions of the cord were seen to be affected indiscriminately. The loose structure of the gray matter was usually most severely demyelinated. The white matter was affected in the lateral, posterior and anterior columns, perhaps slightly more extensively at the edge than in the depths of the cord. No two sections presented the same areas of demyelination, and the pattern of blanching of the white matter was presumably fortuitous. Sometimes extensive patches of demyelination covered the greater part of an entire column,

22. Zamecnik, P. C.; Folch, J., and Brewster, L.: Protection of Animals Against Cl. Welchii (Type A) Toxin by Injection of Certain Purified Lipids, Proc. Soc. Exper. Biol. & Med. **60**:33, 1945.

with islands of relatively normal myelin enclosed within. At other times smaller islands of demyelination were surrounded by extensive expanses of relatively normal myelin. The usual picture, however, as seen best with higher magnification, consisted of clusters of individual sheaths, pale, swollen and refractile. These individual sheaths were separated from one another in the cluster of empty spaces marking the sites of sheaths that had lost their power to stain. The contrast between the nearly normal sheaths and the "demyelinated" ones was striking, the relatively normal sheaths being stained a deep purplish blue and the demyelinated ones remaining completely unstained. Between these two extremes were various degrees of pallor, swelling and refractility, giving a faint purple color to the moderately affected sheaths. Anterior root fibers

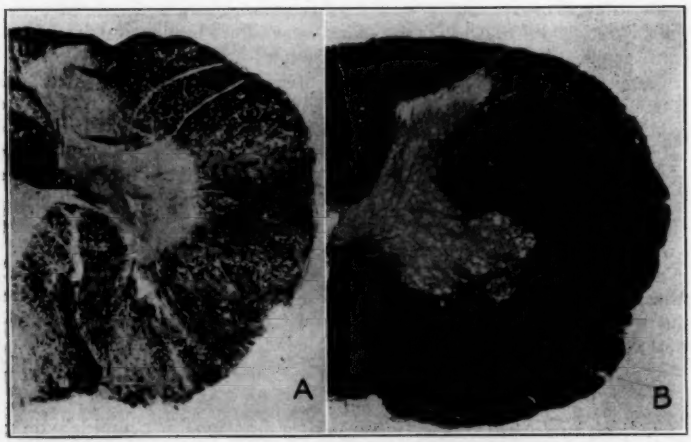



Fig. 1.—Rabbit spinal cord. Frozen section of unfixed tissue cut in a cold chamber and incubated eighteen hours (*A*) in Cl. welchii filtrate (test preparation) and (*B*) in Cl. welchii filtrate with antitoxin (control preparation). Spielmeyer's stain; × 15.

within the cord were sometimes seen to be entirely demyelinated in part of their course and relatively normal in appearance in adjacent regions.

The oil red O preparations presented no fat, but the staining was uneven and patchy and varied in color from pink to mauve, reminiscent of the staining reaction seen with vitamin B complex deficiency.[23] When polarized light was used, the sheaths in the gelatin-mounted preparations were still doubly refractile, even though such sheaths were invisible, or nearly invisible, in corresponding Weil preparations.

23. Gildea, E. F.; Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, New England J. Med. **202**:523, 1930.

Blocks: Blocks of rabbit spinal cord that had been incubated for eighteen hours in a similar, dialyzed Cl. welchii filtrate, fixed and stained, presented a different pattern of distribution of the lesion. A ring of pallor encircled the cord, extending inward from the pial margin anywhere from an eighth to a quarter of the radius of the cord. This blanching sometimes followed blood vessels in, to an even greater depth. On inspection with the high power lens, this pale margin was readily seen to have undergone demyelination, similar to, but perhaps even more complete than, the demyelination seen in incubated sections. The myelin sheaths did not seem to have "dissolved," as far as could be ascertained from Spielmeyer-stained frozen, or Weil-stained pyroxylin, sections.

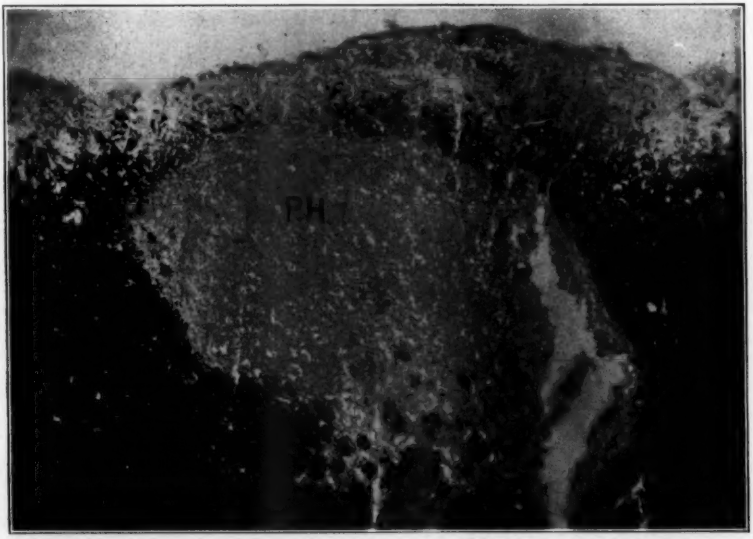



Fig. 2.—Rabbit spinal cord. Frozen section cut from a block that had been incubated eighteen hours in Cl. welchii filtrate. Note the pronounced demyelination around the periphery. *P.H.* indicates the posterior horn. Spielmeyer stain; × 100.

Instead, they appeared to be quite definitely present, but to be pale yellow, almost white, and often lacelike or fringelike in structure. The contrast between the demyelinated margin of the cord, where the enzyme had had access to the tissue, and the ordinary, purple color of the more normal myelin in its depths, where the toxin had not penetrated, was striking (fig. 2). In fact, any one section was not only a "test" section but a "control" section as well, for only the surface and the superficial regions of the block were affected, and the contrast between normal and pathologic myelin sheaths was readily seen in each satisfactory preparation.

Not only were the myelin sheaths affected within the cord, but also the anterior or the posterior root fibers which were exposed to the toxic filtrate likewise lost their myelin sheaths.

Even though the stains for fat gave negative results in these Cl. welchii filtrate preparations, as was to be expected, the products split off in the hydrolysis of lecithin were made perceptible. The phosphate of the choline phosphate radical was made visible, as previously explained, and figure 3 shows such a preparation. On inspection with low magnification the periphery of the section showed up well, since the phosphate had

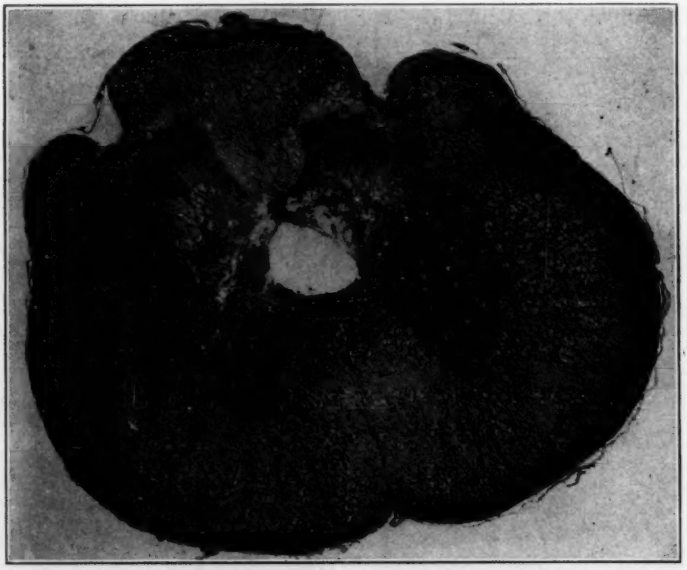


Fig. 3.—Rabbit cord incubated in Cl. welchii filtrate and stained by adaptation of Gömöri's phosphatase method. The black border denotes in this instance the presence of choline phosphate. Counterstained with eosin; × 24.

been trapped in situ. Higher magnification (fig. 4) shows that the phosphate was distributed largely in the conventional location, namely, inside the sheath spaces, and often in large, normal-sized globules of what presumably was formerly lecithin. It will be observed that the test section (fig. 4 *A*) differs from the control section (fig. 4 *B*) not only in the manner already mentioned but also in its presentation of visible axons, in contrast to the control. This is as it should be, since no substrate was added to the controls, and since, of course, control blocks were incubated either without lecithinase or with inactive lecithinase.

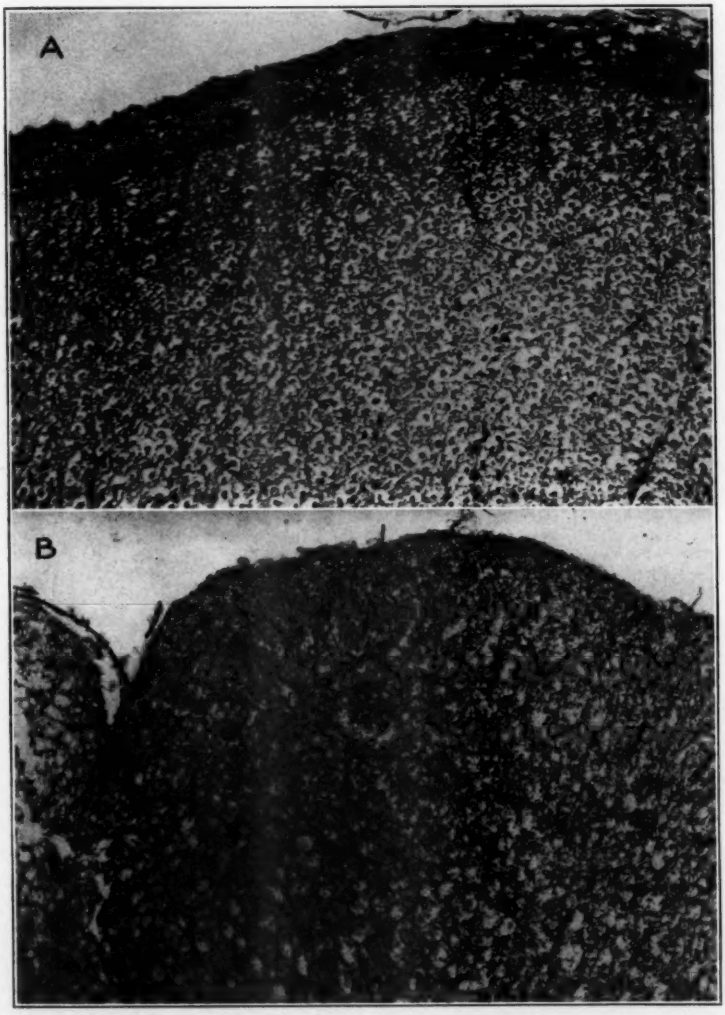



Fig. 4.—*A*, high power view of a field from the edge of figure 3, showing the action of lecithinase on the margin of a block of rabbit spinal cord. *B*, control section, incubated in toxin plus antitoxin. Stained by adaptation of Gömöri's method, counterstained with eosin; × 100.

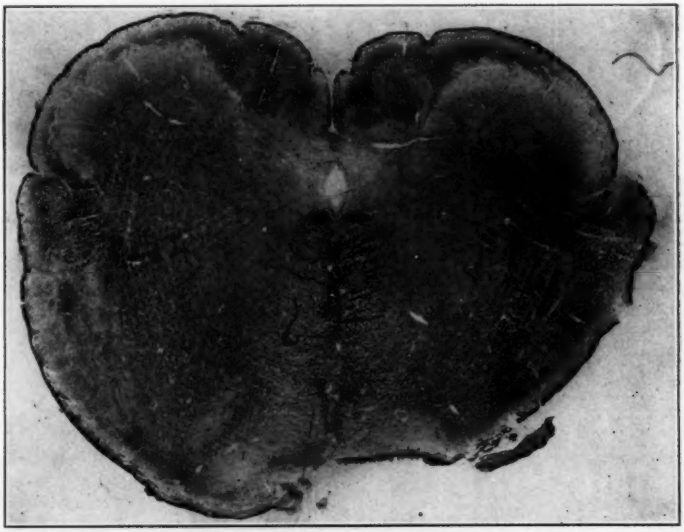


Fig. 5.—Rabbit medulla, incubated twenty-four hours in cobra venom. Loss of myelin is visible as a pale band around the edge beneath the pia, as well as by patches of pallor where the enzyme has penetrated more deeply into the block. Weil stain; × 24.

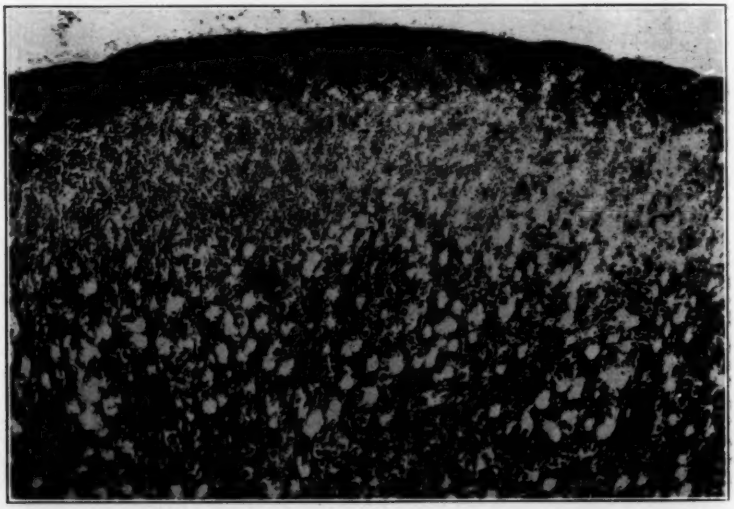


Fig. 6.—Rabbit cord incubated twenty-four hours in cobra venom and stained with oil red O for fat. The loss of myelin is visible across the upper half of the section. The dark band beneath the pia represents bright red fat, which settled around the edge while in a warm, fluid state in the incubator; × 100.

*Snake Venom.*—By way of contrast, other blocks were incubated in cobra venom. This had been done before by Weil,[8] but it was considered necessary to repeat the experiment in the present study in order to have preparations for comparison with the sections incubated with the Cl. welchii toxin. We found that Weil's observations were accurate, and our results duplicated his so far as we did the same thing. Figure 5 shows a section from a block of medulla incubated twenty-four hours in cobra venom (Weil stain), and it is apparent at a glance that peripheral demyelination is present, but that it is not more pronounced than it was in the Cl. welchii filtrate sections. The myelin throughout the section was pale, but around the edge it was severely altered. Unlike the Cl. welchii filtrate preparations in frozen section, the cobra venom blocks presented fat in the sudan III or oil red O stains. In figure 6 this fat can be seen throughout the zone of demyelination, particularly around the very edge just beneath the pia, where it evidently collected while in a warm, fluid condition in the incubator. Examination with polarized light revealed that among the fat droplets in the oil red O stain there were still quite a few anistropic bodies, representing either normal myelin sheath constituents or a "cholesterol–fatty acid mixture."[24]

Besides cobra venom, rattlesnake venom and the venom of the South American B. jararaca were used. Rattlesnake venom presented results similar to, but milder than, cobra venom, but in the small number of tests in which we used the venom of B. jararaca we were unable to produce demyelination.

### OBSERVATIONS DURING IN VIVO EXPERIMENTS

In addition to direct intracerebral injections of Cl. welchii filtrate in 6 rabbits, the toxic filtrate was given by intravenous administration to 10 dogs and a series of mice. Whether the Cl. welchii filtrate was used alone or in combination with Cl. novyi toxin seemed to make little difference. The brain presented no frank, clearcut zones of demyelination as a result of the intravenous administration of the enzyme, and the intracerebral injections were too traumatic to be of value.

### COMMENT

The supposition that the term demyelination does not always connote precisely the same thing is borne out by this investigation. The specificity of reaction of enzymes for their substrates has made it possible to demonstrate that the myelin sheath can be broken down in at least two ways—either by splitting off a fatty acid or by splitting off phosphorylcholine from the phosphatides, particularly from lecithin. If lecithin can be hydrolyzed in a selective manner, by a particular enzyme, it is not unlikely that other constituents of the myelin sheath can be similarly attacked in equally specific ways. Furthermore, various combinations of

24. Lee, B.: Microscopist's Vade-Mecum, ed. 9, edited by J. B. Gatenby and E. V. Cowdry, Philadelphia, The Blakiston Company, 1928, p. 465.

substances may be simultaneously attacked, so that the number of possible ways in which the myelin sheath can be broken down is probably fairly large.

While these in vitro experiments sometimes gave excellent results, the constancy of reproducibility was not always as satisfactory as one might wish. Whether the enzyme itself varied in activity from time to time or whether optimum conditions for its activity have not yet been standardized is not known.

Cobra venom contains not only lecithinase as an enzyme, but cephalinase as well, so that in the present study cephalin as well as lecithin was to some extent affected. Furthermore, the lysolecithin and lysocephalin remaining after the loss of fatty acid are in themselves probably myelolytic, since they both are hemolytic—hence the vigorous myelin breakdown from cobra venom. Milder alterations could have been produced by use of a more selective agent. Similarly, with the toxic filtrate of Cl. welchii, not only lecithin, but possibly to a slight extent sphingomyelin also, was hydrolyzed. However, in the case of Cl. welchii filtrate no further hydrolysis was entered into by the split products of the reaction. It appears, then, that myelin degradations, even though they have been induced by a variety of causes, appear more or less similar in stains of the Weigert type. But histochemical or histophysical studies are of value in further elucidation of the pathologic processes.

While the use of hemolysins in direct action on nerve tissue in vitro has been known to produce demyelination,[25] the use of these substances in vivo has not always been so successful. In the present work the histologic changes in the brains of dogs that had been given Cl. welchii filtrate intravenously were mild and equivocal. We have said that they were absent. They were not clearcut like those reported by Frazer and his co-workers [9] after intramuscular injection. Moreover, Putnam, McKenna and Morrison,[2] following the technic of Claude,[26] injected another hemolysin, tetanus toxin, into dogs and succeeded in producing demyelination in only 2 animals of a series of 80.

The negative electrical charge of tetanus toxin puts it at once, according to Friedemann,[27] in that group of substances which are unable to penetrate the blood-brain barrier. That tetanus toxin reaches the central nervous system by way of the motor nerves has also been shown by Friedemann, Hollander and Tarlov.[28] It is interesting, in the light of this observation, that the lesions produced by Putnam, McKenna and Morrison, after intraperitoneal administration of tetanus toxin, were in the spinal cord and brain stem.

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25. (*a*) Flexner and Noguchi.[7] (*b*) Frazer and associates.[9] (*c*) Weil.[8]

26. Claude, H.: Myélite expérimentale subaïgue par intoxication tétanique, Arch. de physiol. norm. et path. **29**:843, 1897.

27. Friedemann, U.: Blood-Brain Barrier, Physiol. Rev. **22**:125, 1942.

28. Friedemann, U.; Hollander, A., and Tarlov, I. M.: Investigations on Pathogenesis of Tetanus, J. Immunol. **40**:325, 1941.

In the present investigation we were evidently unable to produce passage of the alpha toxin of Cl. welchii through the blood-brain barrier to any considerable extent. Even if the alpha toxin carries a positive charge, it may be unable to penetrate the capillary wall, for much of the active enzyme is promptly bound by the lecithin of the pellicles of the red blood corpuscles, or even by the lecithin of the capillary wall itself. If the intravenous dose was large, in order that an excess of lecithinase might be left to exert its myelolytic effect after the barrier had been breached, the lethal effect was all the prompter and the survival time too short for myelolysis to occur except as a postmortem phenomenon.

The presence of hyaluronidase apparently did not facilitate the in vivo action of lecithinase on the brain, since the Cl. welchii filtrate contained an appreciable amount of hyaluronidase, in addition to the lecithinase.

## SUMMARY AND CONCLUSIONS

Sections or blocks of spinal cord and brain of laboratory animals were incubated in Cl. welchii filtrate (consisting principally of alpha toxin), or in various snake venoms, and were then prepared for histologic study. In addition, Cl. welchii filtrate was injected intracerebrally into rabbits and intravenously into dogs, rabits and mice.

In the in vitro tests, demyelination, as indicated by the Spielmeyer or the Weil stain, was produced by Cl. welchii filtrate, cobra venom and rattlesnake venom.

Fatty degeneration, as shown by the oil red O stain, was found in the cobra venom preparations, but not in the Cl. welchii filtrate preparations.

Free phosphate ions, as detected by Gömöri's phosphatase stain, were found in the Cl. welchii filtrate preparations, and a new use for this histochemical technic was introduced. Whereas previously, according to this technic, the presence of an enzyme in a tissue has been detected by the addition of a substrate, in the present modification the presence of a substrate (lecithin) in the tissue is detected by the addition of an enzyme (lecithinase) capable of attacking it.

In the in vivo tests, the intravenous injections produced no loss of myelin.

It is maintained, therefore, that not only can the myelin sheath be broken down by enzymatic action but also that it can be broken down in more than one way, that is, that "demyelination" may not always be precisely the same process.

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# TOPOGRAPHIC DISTRIBUTION OF PLAQUES IN THE SPINAL CORD IN MULTIPLE SCLEROSIS

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COPENHAGEN, DENMARK

THE PRESENT work is an attempt to define the topographic distribution of plaques in the spinal cord in multiple sclerosis, thus contributing to the solution of the old and important question of the possible relation of vascular territories to the formation of plaques.

Ever since Rindfleisch [1] (1863) first gave an account of the topography and morphology of plaques there has been constant controversy concerning this problem, which has not yet been definitely solved. Its significance has been realized for many years, and it is possible to say as did Rossolimo [2] (1904) that it is a question of eminent importance to the understanding of the pathogenesis of multiple sclerosis. Prominent German neuropathologists (Pette,[3] 1928; Hallervorden,[4] 1940) have stated the opinion that no evidence has been given of a relation of vascular territories to the localization of plaques. Hallervorden [4] stated that plaques are related neither to arterial territories nor to venous territories. In the United States, Hassin [5] disagreed with the vascular theories, and recent American attempts to solve the problem of cerebral plaques (Dow and Berglund [6]) have led to the conclusion that cerebral plaques are not always centered around a vessel. A number of authors since Rindfleisch,[1] however, have accepted the theory of peri-

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1. Rindfleisch: Histologische Detail zu der Degeneration von Gehirn und Rückenmark, Arch. f. path. Anat. u. Physiol. **26**:474, 1863.

2. Rossolimo, G. J.: Multiple Sklerose, in von Flatau; Jacobsohn, E., and Minor, L.: Handbuch der pathologische Anatomie des Nervensystems, 1904, vol. 1, p. 691.

3. Pette, H.: Ueber die Pathogenese der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **105**:76, 1928.

4. Hallervorden, J.: Die zentralen Entmarkungskrankheiten, Deutsche Ztschr. f. Nervenh. **150**:201, 1940.

5. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, ed. 2, New York, Paul B. Hoeber, Inc., 1940; Studies in the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:589 (May) 1922; Pathological Features of Multiple Sclerosis, ibid. **38**:713 (Oct.) 1937.

6. Dow, R. S., and Berglund, G.: Vascular Pattern of Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **47**:1 (Jan.) 1942.

vascular localization of plaques. Strähuber [7] in 1903 found nineteen authors in favor of this theory and ten against it. Later important works (Anton and Wohlwill,[8] 1912; Dawson,[9] 1916; Putnam,[10] 1936, 1937; Döring,[11] 1940) have demonstrated the perivenous localization of certain plaques.

In modern experimental disseminated encephalomyelitis the perivascular localization is a prominent phenomenon of the pathoanatomic picture, and this phenomenon has been identified with the changes in multiple sclerosis. Antagonists of the vascular theory still stress the difference between the foci in perivenous encephalomyelitis and those in multiple sclerosis; the former cover the vessels like a mantle for a long distance, while the latter surround the vessels only for a short distance and tend to spread out more rapidly than do the former.

Only few attempts have been made to investigate a long continuous portion of the central nervous system, for example, the spinal cord. One such study was presented by Falkiewicz [12]; unfortunately, the data were not given in sufficient detail. Falkiewicz concluded that a perivascular localization is not evident for all plaques, particularly the wedge-shaped plaques of the posterior column.

The difficulty in clearly defining the topography of cerebral plaques arises from the complicated and uncertain vascular pattern of the brain. The vascular pattern of the cord is relatively clear. Recent work in this field (Suh and Alexander,[13] 1939; Herren and Alexander,[14] 1939) has supplemented the old and thorough investigation of Kadyi [15] especially

7. Strähuber, A.: Ueber Degenerations- und Proliferationsvorgänge bei multipler Sklerose des Nervensystems, Beitr. z. path. Anat. u. z. allg. Path. **33**:409, 1903.

8. Anton, G., and Wohlwill, F.: Multiple nicht eitrige Encephalomyelitis und multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:31, 1912.

9. Dawson, F. W.: The Histology of Disseminated Sclerosis, Tr. Roy. Soc. Edinburgh **50**:517, 1916.

10. Putnam, T. J.: Studies in Multiple Sclerosis: Similarities Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, Arch. Neurol. & Psychiat. **35**:1289 (June) 1936. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, ibid. **38**:1 (July) 1937; Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," ibid. **37**:1298 (June) 1937.

11. Döring, G.: Zur Pathogenese der Herdbildung bei der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **150**:146, 1940.

12. Falkiewicz, T.: Zur Pathologie der multiplen Sklerose, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **28**:172, 1926.

13. Suh, T. H., and Alexander, L.: Vascular System of the Human Spinal Cord, Arch. Neurol. & Psychiat. **41**:659 (April) 1939.

14. Herren, R. Y., and Alexander, L.: Sulcal and Intrinsic Blood Vessels of Human Spinal Cord, Arch. Neurol. & Psychiat. **41**:678 (April) 1939.

15. Kadyi, H.: Ueber die Blutgefässe des menschlichen Rückenmarkes, Lemberg, Gubrynowicz & Schmidt, 1889.

concerning the intramedullary vascular system; and clinical experience seems to confirm the vascular theory, at any rate with regard to the arteries (Margulis [16]; Zeitlin and Lichtenstein [17]; Ornsteen [18]; Chung [19]; Winkelmann and Eckel,[20] and others, to which papers the reader is referred).

### VASCULAR SYSTEM OF THE SPINAL CORD

The pattern of arborization of the intramedullary vessels will be described only briefly (Suh and Alexander, Herren and Alexander). The spinal cord is supplied with blood through six to eight radicular arteries, which are unsymmetrically distributed. On the ventral side of the cord there arises an anterior arterial trunk, from which the branches pass upward in the anterior median fissure. In the depth of the fissure the artery passes to either side below the anterior white commissure; from there it continues into the cord substance, branching into the paramedian vascular network and forming an anastomosis in the upper and lower segments. Another branch continues into the anterior gray column and the column of Clarke, while other branches supply the ganglion cells of the anterior and lateral horns, continuing into the anterior and lateral columns. The artery in the anterior median fissure (fig. 13 *A*) thus supplies the entire cord with the exception of the posterior columns, which are supplied by an artery perforating the cord together with the posterior root. The posterior horn and the posterior commissure are also supplied by the branches of the anterior artery.

The venous drainage is effected somewhat differently. The vein of the anterior median fissure carries blood only from the white matter along the anterior median fissure and from both sides (fig. 13 *B*). Centrally, this vein is formed by anastomoses about the central canal. This venous system receives a large branch from the central portions of the dorsal two thirds of the lateral columns (fig. 13 *B* and *E*) and branches from the gray matter. The remainder of the lateral columns is drained by smaller radial veins, which run out into the great subarachnoid venous network on the surface of the spinal cord. This distribution also applies to the ventral columns, except for the portion lying sym-

16. Margulis, M. S.: Pathologische Anatomie und Klinik der akuten thrombotischen Erweichungen bei spinaler Lues, Deutsche Ztschr. f. Nervenh. **113**:113, 1930.

17. Zeitlin, H., and Lichtenstein, B. W.: Occlusion of the Anterior Spinal Artery, Arch. Neurol. & Psychiat. **36**:96 (July) 1936.

18. Ornsteen, A. M.: Thrombosis of the Anterior Spinal Artery, Am. J. M. Sc. **181**:654, 1931.

19. Chung, M.: Thrombosis of the Spinal Vessels, Arch. Neurol. & Psychiat. **16**:761 (Dec.) 1926.

20. Winkelmann, N. W., and Eckel, J. L.: Focal Lesions of the Spinal Cord, J. A. M. A. **32**:1919 (Dec. 3) 1932.

metrically on each side of the anterior median fissure. The gray matter is also drained by many independent branches running directly to the surface. In the dorsal columns a large ventral vein is formed in the midline, and centrally it receives branches from the posterior commissure, thus forming a fork of large branches. This central vein drains a wedge-shaped field, of which the base is formed by the two large veins of the posterior commissure and the apex points toward the surface of the cord. This vein thus drains symmetric portions of the cord. The remainder of the dorsal column is drained by smaller, independent radial veins running out to the dorsal surface of the cord. In the cervical portion of the cord two larger radial veins arise on each side of the centrally placed truncus venosus posterior. The posterior root and Clarke's column are drained by a large radial vein, which takes blood from the marginal portions of the white substance (fig. 13 *B*). All the intramedullary veins of the cord pass either to the surface or to the central venous network and bifurcate after a short, spokelike course into ascending and descending branches. The place of division is at about the same level for the various radial veins; in the cervical portion of the cord, for example, the five radial veins bifurcate in the posterior column always at the same depth and approximately at the same level.

Suh and Alexander divided these venous systems into orders of different magnitudes and stated that a kind of valvular system is at work at the places of bifurcation.

Figure 13 *E* shows schematically the glial pattern with special reference to the vessels. The diagram was drawn from a cross section of the spinal cord of a patient with multiple sclerosis, in which disease the glial pattern may be seen clearly (isomorphic proliferation). The glia forms a ring around the central canal; anteriorly the glia extends toward the vessels of the anterior median fissure. Dorsally and horizontally may be seen the vascular system of the posterior commissure, converging toward the posterior septum. Laterally is seen a junction of veins between the lateral and the posterior horn. From here a number of glial septums and vessels radiate into the inner portion of the lateral column. In the description of the individual cases this point is named the "axilla."

The diagram closely corresponds to figure 6 of Suh and Alexander.[18] The veins seem to form independent systems. Anastomoses are seldom seen in the transverse plane between the larger radial veins and their branches except for an occasional valvular vessel (Suh and Alexander) connecting the venous system around the central canal (the anterior venous system of the cord) with the posterior system. No amastomoses have been described between the central vein in the posterior column

and the radial veins in the more lateral parts of the posterior column. The radial veins in the posterior columns of the cervical portion of the cord never form anastomoses, and their finest branches always join the same system.[5] Only in the midline are anastomoses seen in longitudinal section between the large central veins of the upper and lower segments of the posterior column. This applies also to the venous system of the lateral columns. The arborization of the veins of the white matter might be compared to a tree with independent branches; no connections are seen between one tree and another.

## MATERIAL AND METHODS

The topography of plaques in the spinal cord was studied in 8 cases of multiple sclerosis in which the greater part of the spinal cord, or large portions of it, were prepared for examination. A stain was selected which gave a clear picture both of the shape and extent of the plaques and of the localization and course of the vessels. Paraffin blocks were used, 161 blocks in all, and Mallory's connective tissue stain was chosen to make possible the study of endovascular changes. This point was considered especially significant in the light of Putnam's theory of thrombosis. Serial sections 7 microns in thickness were used throughout. The distribution in the individual cases is briefly summarized.

## REPORT OF CASES

CASE 10.—A woman aged 33 had had two severe attacks of multiple sclerosis at an interval of three years. After the second attack recovery was incomplete; new symptoms developed six months later, and her condition deteriorated. Landry's ascending paralysis developed, and the patient died. Autopsy revealed typical plaques throughout the central nervous system.

The cord was divided into 20 parts, beginning in the central region of the cervical portion and continuing distally to the middle of the lumbar region. Every fifth section was stained. Figures 1 to 4 illustrate the shape of the plaques, fully outlined, as well as the more netlike figures. The numbers are those of the sections mounted. In the interest of brevity, cross sections are shown only from the regions where some change occurs, or to illustrate growth and confluence of plaques. In the text, the terms spongy plaques and gitter plaques are used in referring to the structure, which will be described later.

The plaques were localized in this cord according to a certain system: In the first 10 of the 20 parts (half of the entire cord) the plaques were situated in the dorsal one-half to two-thirds of the lateral columns, with the exception of a few in the central portion of the posterior columns and in the anterior columns along the anterior median fissure. In parts 11, 12, 13 and 14 the ventral portion of the lateral columns was free from plaques, before any other parts. In the last 5 parts only the plaques appeared to be scattered irregularly throughout the lateral and anterior columns, whereas in the whole cord the central portion of the posterior columns seemed to be the site preferred.

The localization of plaques in the majority of sections of the cord could be compared to a butterfly, the wings being the plaques of the lateral columns, and the trunk, the central plaques, with the head in the middle of the posterior columns and the legs the plaques of the anterior medial fissure.

The gray matter was broken up to a great extent by plaques continuing unchecked from the column into or through the gray matter. This applied chiefly to the posterior horn, which was always involved by the plaques of the lateral

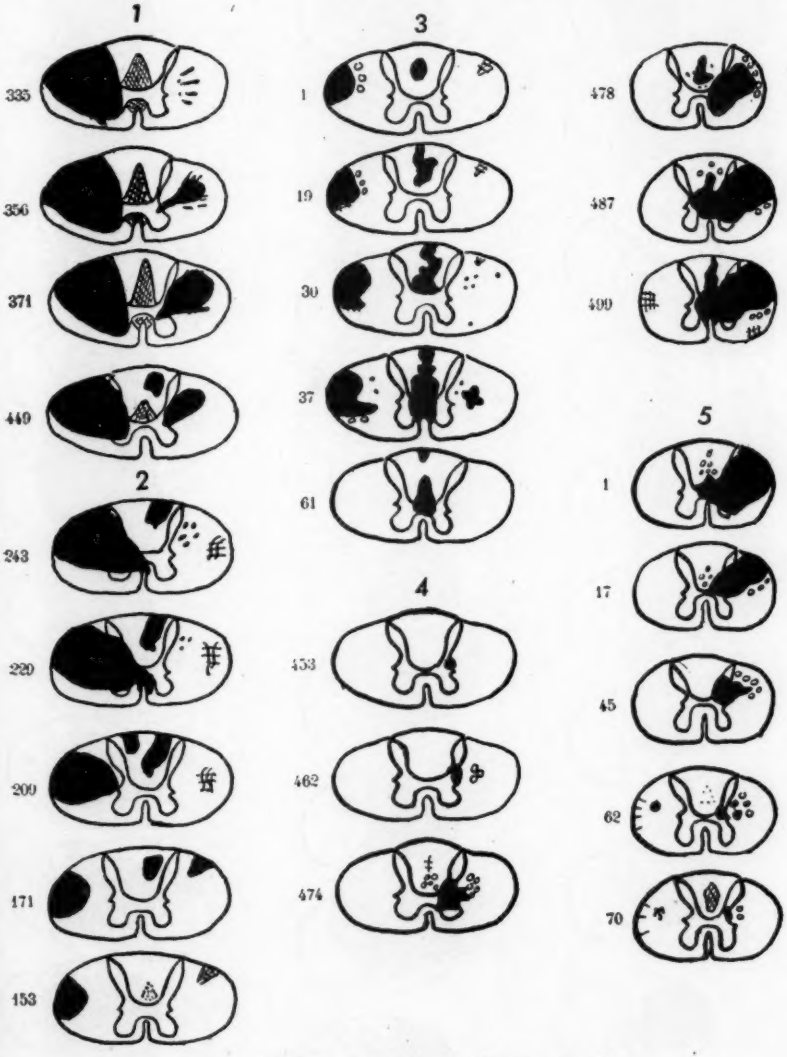


Fig. 1.—Sections of cord (parts 1-5) in case 1.

columns; these plaques usually extended slightly into the lateral portions of the posterior columns. Finally, infiltration around the central canal, forming central plaques, was observed frequently.

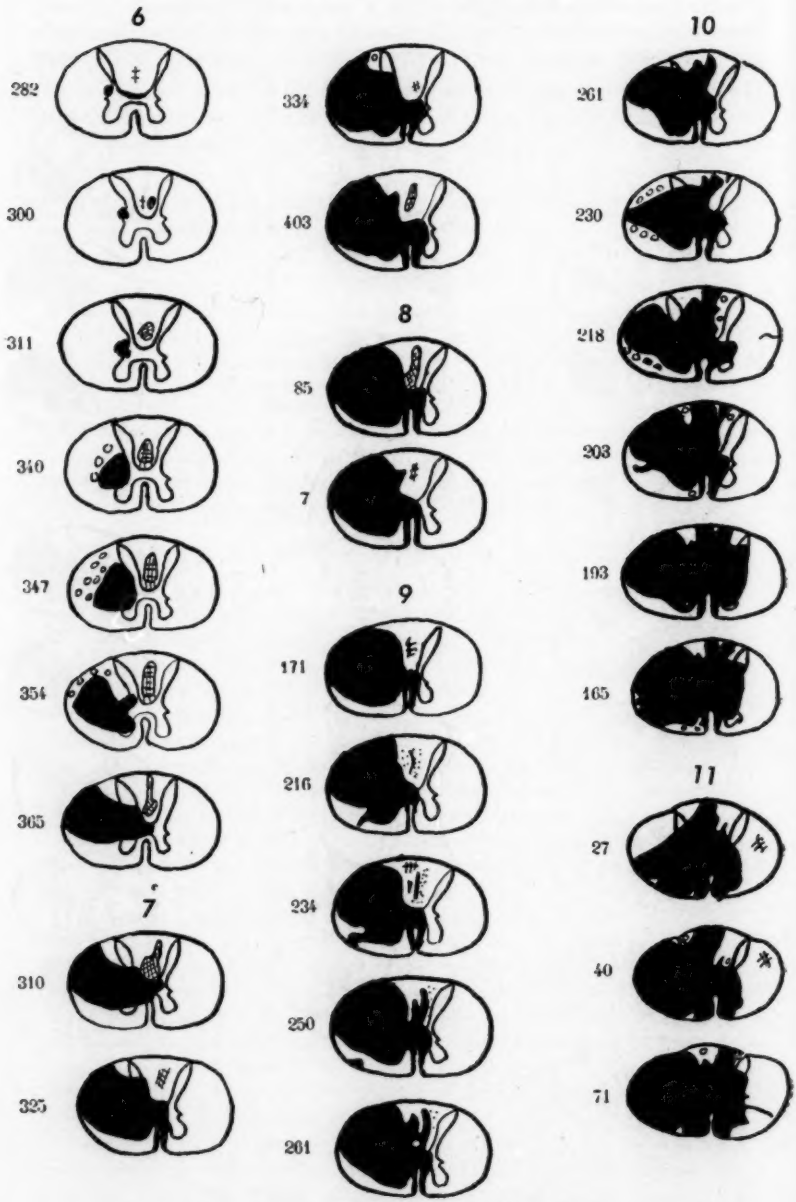


Fig. 2.—Sections of cord (parts 6-11) in case 1.

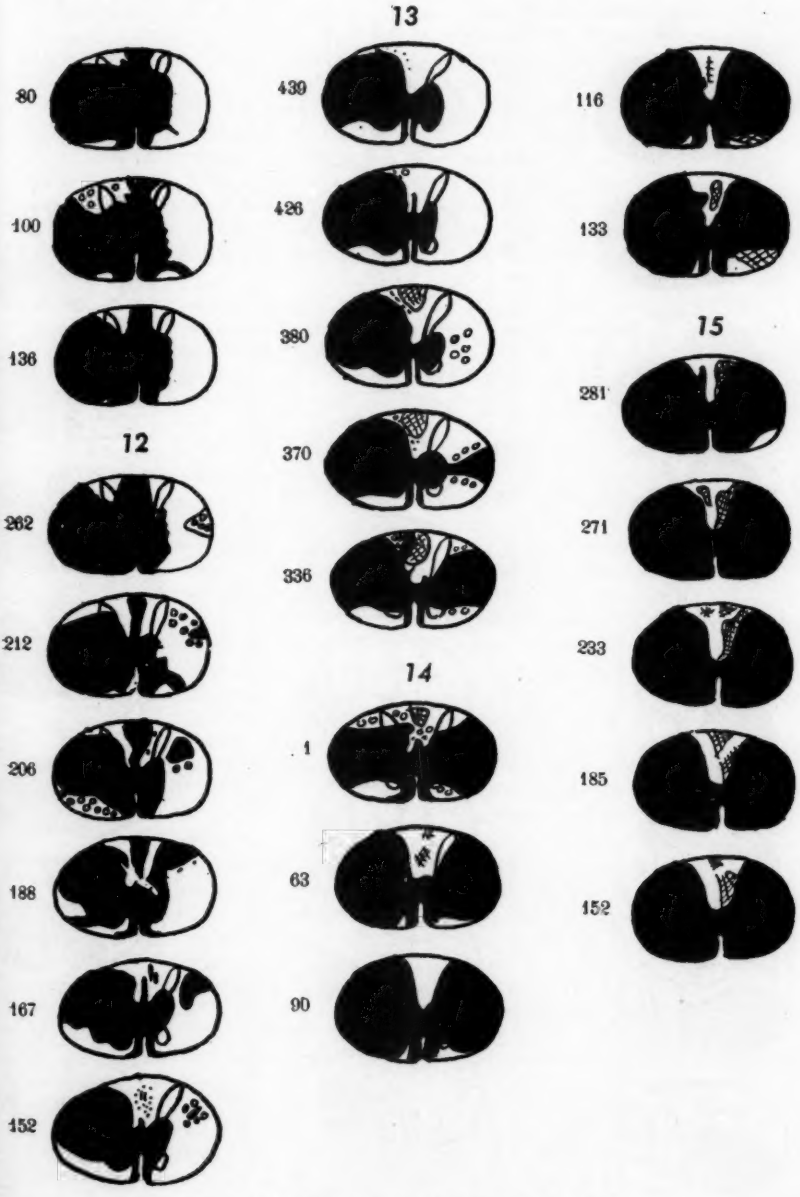


Fig. 3.—Sections of cord (parts 12-15) in case 1.

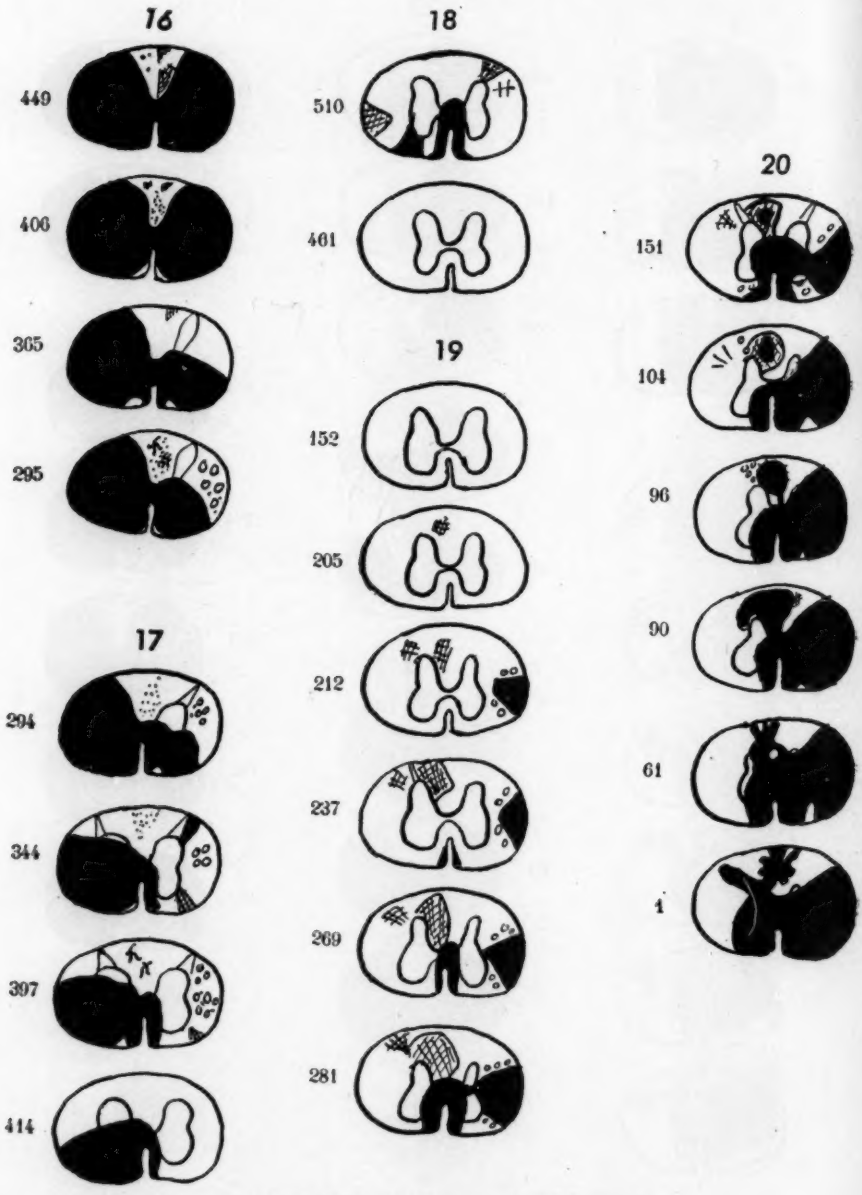


Fig. 4.—Sections of cord (parts 16-20) in case 1.

The shape of the plaques could be explained only by the vascular pattern of the cord, especially that of the veins. The principle is briefly outlined below, and a more detailed analysis is described in connection with the structure of the plaques.

Easiest to survey are the plaques of the posterior columns. As previously mentioned, the plaques of the posterior columns were as a rule situated centrally. At the level of their maximum extent they were elongated (part 3), oval (part 6), wedgelike (parts 1, 4, 10 and 11) or fungus shaped (parts 12 and 20). More laterally placed plaques might occur, but they were small and rare. The plaques might extend to both sides, so that most of the posterior columns were involved; but as a rule the lateral peripheral portions were spared, forming a free peripheral sector.

Cranial and caudal to its largest portion the plaque tapered, lying within the substance of the posterior system, clear of the surface, as well as of the gray matter. The plaque, in other words, became T shaped, the trunk of the *T* being the main part of the plaque and a central, large radiating vein, and the cross stroke corresponding to the ascending and descending branches of this vein (parts 3, 11 and 33).

The plaques of the anterior columns were also clear, lying symmetrically as bands along the anterior median fissure. They are seen in parts, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19 and 20. In parts 1 and 6 are normal anterior columns; in part 15 are transverse plaques, which make it impossible to distinguish the changes in the paramedian part of the cord from those in the remaining parts. The anterior columns may be involved in the development of plaques by extension from the lateral columns, but as a rule they are free from plaques before the other columns. In the lumbar portion of the cord only, isolated plaques were observed in the anterior columns, independent of the anterior median fissure.

The vein of the anterior median fissure is the central vein in the plaques of the anterior column. Centrally this vein unites with the wreath of longitudinally running veins surrounding the center of the cord. These vessels are fed from branches in the vicinity of the column systems. The formation of a larger branch from the dorsal part of the lateral columns is frequently observed, as the ventral part drains to the periphery only. This system is also connected with the veins at the dorsal side of the cord through large valvular vessels, which were frequently observed in this case.

This case shows that the paramedian plaques do not occur alone. When this seems to be the case, it is because plaques are not followed from one end of the cord to the other. In part 1 is seen, for example, how "gitter" plaques around the base of the anterior median fissure dorsally continue around the central canal and on to the middle of the posterior column. Further, in part 3, paramedian plaques are seen continuing dorsally through the gray matter and directly into the posterior column. The same thing is clearly seen in the caudal portion of part 17, in the cranial portion of part 18, farther caudally in part 19 and also in part 20. In these parts are seen examples of confluence of plaques in the lateral column and paramedian plaques, which partly fade away along the fissure, and partly occur in the opposite order, beginning peripherally around the apex of the fissure, from where it may be followed along the fissure into the central gray matter and on into plaques of the lateral columns. Similar examples will be mentioned in the description of plaques of the lateral columns.

In cross section the typical plaques of the lateral columns are seen lying like a broad fan in the dorsal half of the lateral columns with the base of the fan

immediately under the surface. In many places it may be seen how the apex of the fan continues into the gray matter, where eventually the central canal is encircled and from whence the plaques then continue along the anterior median fissure. In cross section this plaque is sharply defined, with its anterior demarcation following closely the course of the vascular septums in a frontally convex curve, while the posterior border penetrates the posterior horn on its short course to the posterior column. Occasionally these borders are broken by an extension toward the periphery, always lying close around a vein (parts 9, 10, 13, 14 and 15). These extensions usually leave the main plaque, and they must be considered as independent small plaques. This is clearly apparent from the detailed analysis given below.

In longitudinal section the shape of these plaques of the lateral columns was rather irregular, but also here a definite principle seems to be predominant. Anton and Wohlwill compared all plaques in the central nervous system to elliptoids, a description which fits well the plaques of the lateral columns. The shape of plaque *2* in parts 1 and 2 may serve as an example.

The process begins dorsally and centrally in the left lateral column with several perivascular foci, which gradually fuse into a larger wedge-shaped or fan-shaped focus in section. At its maximum extent it invades the gray matter as far as the anterior median fissure, after which it recedes, breaking up into numerous small perivascular foci still farther dorsally in the left lateral column around small vertical vessels. The enormous plaque *1* in the right lateral column reaches its maximum in part 2, and is here seen communicating ventrally with the plaques of the anterior median fissure. As described, this plaque recedes at the point where a large vein surrounded by parts of a plaque crosses the base of the right anterior horn on its way to the anterior median fissure. The plaque extends toward the surface of the right lateral column, where it gradually fades away along the veins.

Analysis of plaque 13 in part 4, plaque 22 in part 6, plaques 31 and 32 in part 12, plaque 34 in part 13, plaque 44 in part 19 and the zones of progression in the enormous plaque in the center of the cord are all evidence of the same thing: progression along veins coursing vertically within the white matter. Consequently, the shape of these plaques depends closely on the course of the veins. This being chiefly vertical, it is evident that the plaques must grow lengthwise, to reach their greatest diameter in the places where the veins turn in a radial direction at right angles to the longitudinal axis. The perivascular location of the zones of degeneration is demonstrated repeatedly in serial sections. (The narrow "encephalitic" zones have been mentioned.) The somewhat broader bands resemble puff sleeves—so-called perivascular sleeves—and may be seen more frequently than the narrow bands. In the literature, especially in German writings, it is often stated that such long, band-shaped perivascular proliferations of microglia are characteristic of postvaccinal encephalomyelitis, whereas the small sclerotic plaques surround the vessel for a shorter extent only. In this case the zones extended along vessels as far as these maintained a certain diameter, but always along venules or veins. This is not true in all cases however.

CASE 2.—A woman aged 56 had first intermittent symptoms; later, after her menopause, the symptoms gradually progressed, during a period of twenty-two years. Autopsy showed typical multiple sclerosis.

The cord was divided into 35 blocks, beginning in the cervical region and continuing to the lower lumbar region. Each single block was subdivided into 20 to 30 parts.

This case was of considerable interest. On a preliminary survey, it appeared difficult to determine the relation of plaques to vessels, since the changes were extensive throughout the entire cord and only a few isolated plaques were to be seen. Even the diagnosis of multiple sclerosis was uncertain. An unbiased observer would not call the lesions seen in the Mallory and Holzer preparations disseminated, as the changes were confluent in a longitudinal as well as a transverse direction. It may be seen that the localization of the pathologic changes follows a principle which may be accepted as law. The alterations—this word includes anything abnormal seen in the preparation, especially the glial changes—were observed in the posterior columns centrally, and within a space separated from the surface by a band of varying width, the radius of its dorsal limitation being slightly less than that of the dorsal curve of the cord, and the band decreasing to a regular wedge always located centrally. Consequently, the peripheral and lateral portions of the posterior columns were generally not involved. In the lateral columns the changes occurred in the dorsal two thirds of the cord, with a definite regularity in the "axilla," i. e., in the angle between the posterior and the lateral horn. From this point the plaques radiated in fan shape, being limited by the vascular septums toward the pial surface, so that a zone of varying size was left sharply limited from the plaque. Almost invariably the anterior parts of the lateral columns and of the anterior columns except the paramedian zone were spared.

In general, the localization of the plaque corresponds to that of the first case. But in case 2 the lumbar region was an exception to the general rule, with changes in the anterior parts of the lateral and anterior columns; this, however, was not constant, and the alterations were not pronounced.

A more detailed analysis of the relation of the plaques to the vessels is difficult, not only because the alterations in this are are so extensive but also because the hyperemia is much less than in case 1. On closer observation, however, there are several points of resemblance with the plaques described in case 1.

In part 1 is seen a classic spongy plaque localized in one lateral column and on both sides of the anterior median fissure.

Part 8 shows a plaque of similar contour, being here only "net" plaque. Another is seen in part 12. In part 15, in the central portion of the posterior column may be seen a low wedge continuing anteriorly to the base of the anterior median fissure. In parts 17 and 19 is found a central perivascular area of gliosis in the posterior columns; in parts 21 and 23 is essentially the same picture, and in part 32 the plaque formation follows closely the vascular arborization in the posterior columns.

The localization of the changes seemed to a certain degree systematized in a way which can be explained only by the venous patterns. Throughout this cord the changes seemed to increase and decrease regularly in diameter. At levels at which the changes reached their maximum, extending throughout the entire cord, great vessels were seen radiating from the center to the surface of the cord. At the levels where only small changes were seen centrally in the columns, only small vessels were observed in cross section.

The interpretation of this systematization is possible only with knowledge of the anatomy of the spinal veins. The short, wide radial veins divide into an ascending and a descending branch, and the maximal

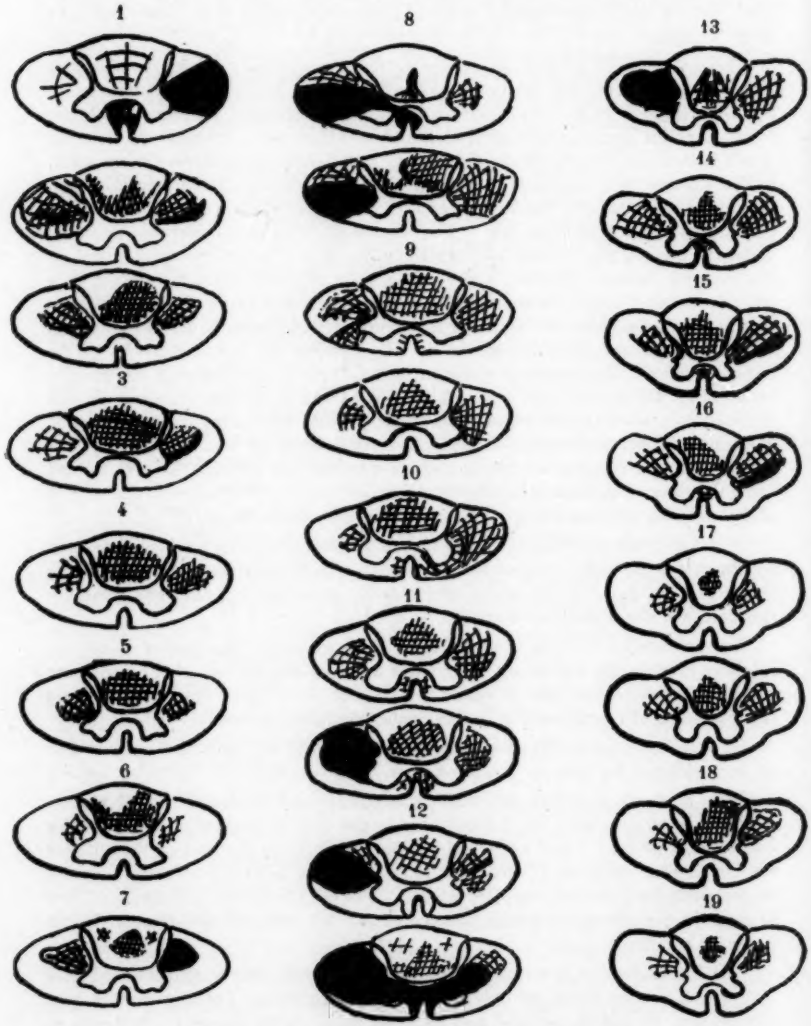


Fig. 5.—Sections of cord (parts 1-19) in case 2.

changes are reached at the level of this large collecting vein. The central changes in the substance follow the ascending and descending branches. It was not possible in this case, as in case 1, to prove this in each

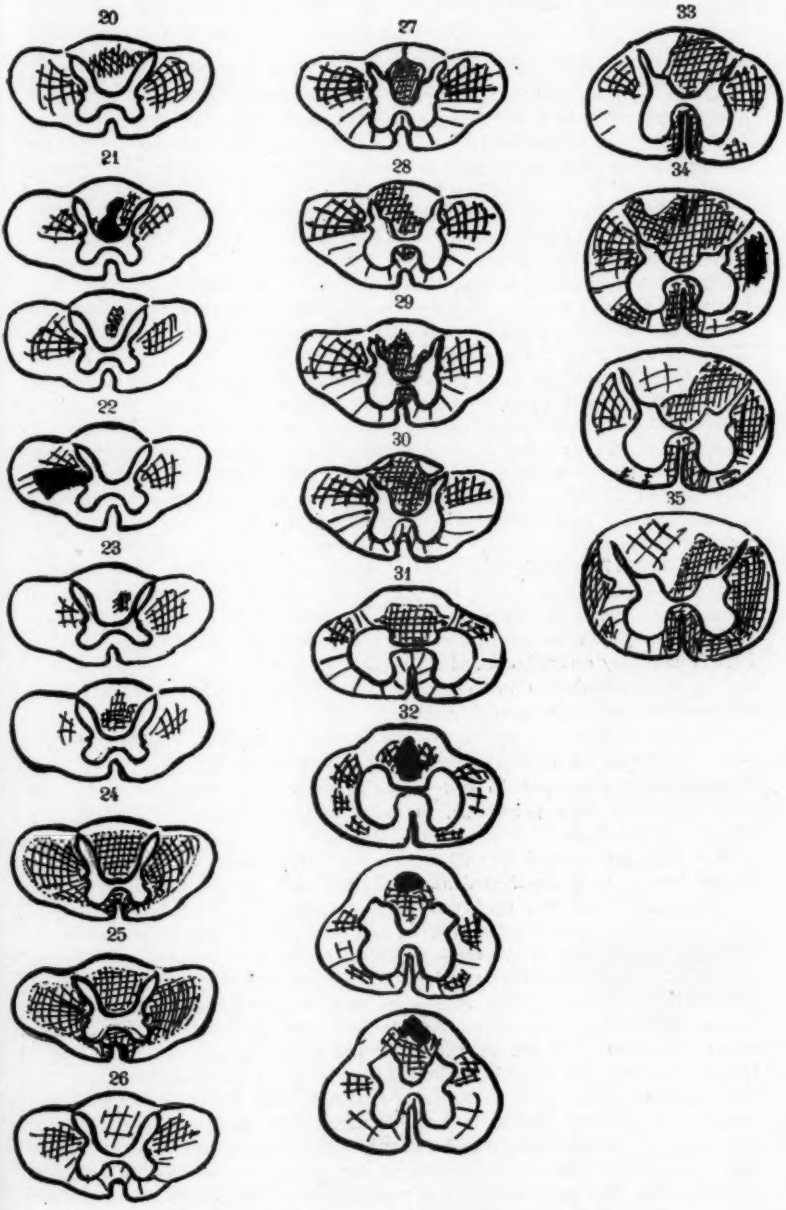


Fig. 6.—Sections of cord (parts 20-35) in case 2.

plaque, since the distance between the sections is too great (20 to 25 sections per part), but the relation described was observed so frequently that the theory must be considered correct.

CASE 3.—A man aged 51 had gradually progressive symptoms of multiple sclerosis from 1926 to 1940. Autopsy showed classic multiple sclerosis.

The cord was divided into 22 blocks and each paraffin block again into about 20 sections, beginning in the upper cervical portion and continuing into the upper lumbar region.

Several Mallory stains of this cord were unsatisfactory, as the paraffin blocks after staining of the first sections from each block, were kept for several years before the serial sectioning was resumed. The Mallory staining of the old paraffin blocks occasionaly failed, possibly owing to deficient fixation. The sections from the deeper parts of blocks were indistinct, but details could still be studied. The changes showed marked uniformity, since this case apparently represented an earlier stage than case 2 and the subsequent cases.

As in case 2, but to a more pronounced degree, the pathologic alterations were localized in the central part of the posterior column and extended posteriorly in both lateral columns from the "axilla" and along the anterior median fissure. In blocks 1 and 22 only the changes were more diffuse but still followed the same principle. Both these blocks showed almost complete transverse sclerosis, but with classic localization of the most pronounced changes: centrally in the posterior columns, dorsally in the lateral columns and on both sides of the anterior median fissure.

From block 7 to block 18 it was clearly evident how the gliosis was formed around the central deep vertical veins in the substance of the cord with an occasional perivascular prolongation along the radial vessels in the midline, sometimes as far as the pia. This is the manner in which the gliosis increases by extension, later fading away centrally around the vertical branches.

The same distribution was observed in the lateral columns, while the paramedian gliosis ventrally was only slight.

Throughout this cord was apparent a pericentral gliosis, with the numerous cross sections of the vessels in the central portion of the corona.

CASE 4.—A man aged 56 had gradually progressing symptoms from 1930 until his death, from pneumonia, in 1938. Autopsy showed typical multiple sclerosis of the brain.

The cord was divided into 20 continuous portions, each of which was subdivided into 20 to 30 serial sections. Mallory's stain was used.

The condition of this cord was relatively clear and supplemented that in case 3. In the posterior columns were seen two large plaques of typical localization and shape, and in the cervical portion of the cord the maximum extent reached was in the cranial part of block 2, where practically the whole posterior column was sclerotic. Above and below this level the plaque was limited to the central portion, with sharp demarcation from the lateral portions. The cranial extension could not be followed. The caudal extension continued in a typical way into the central portion of the posterior columns, free from the surface as well as from the gray matter, and extended along the vertical central veins and their anastomoses into parts 4 and 5, where only small perivascular foci of hypertrophic glia were observed. A strange configuration is seen in part 3, where the plaque crosses the central portion of the posterior columns, like a bridge, extending into the gray matter as a continuation of the glioses of the lateral columns. The gliotic transverse glial septum forming the cross stroke of the well known H of the cord is also hyperplastic.

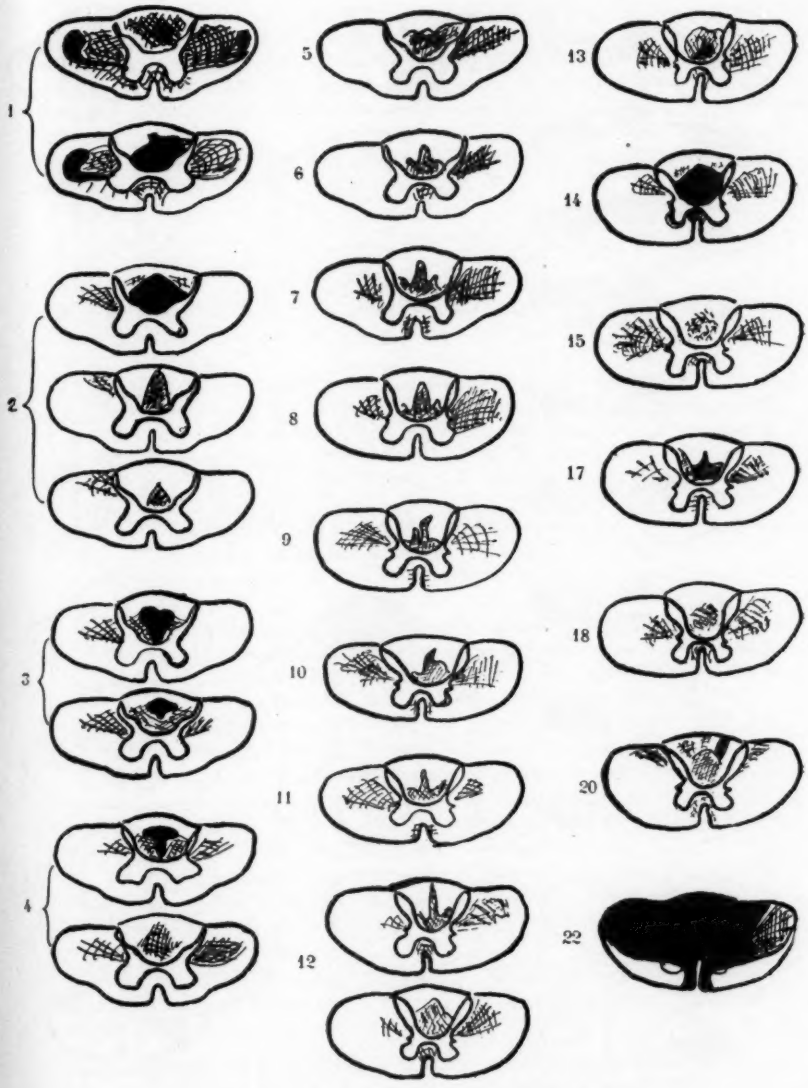


Fig. 7.—Sections of cord in case 3.

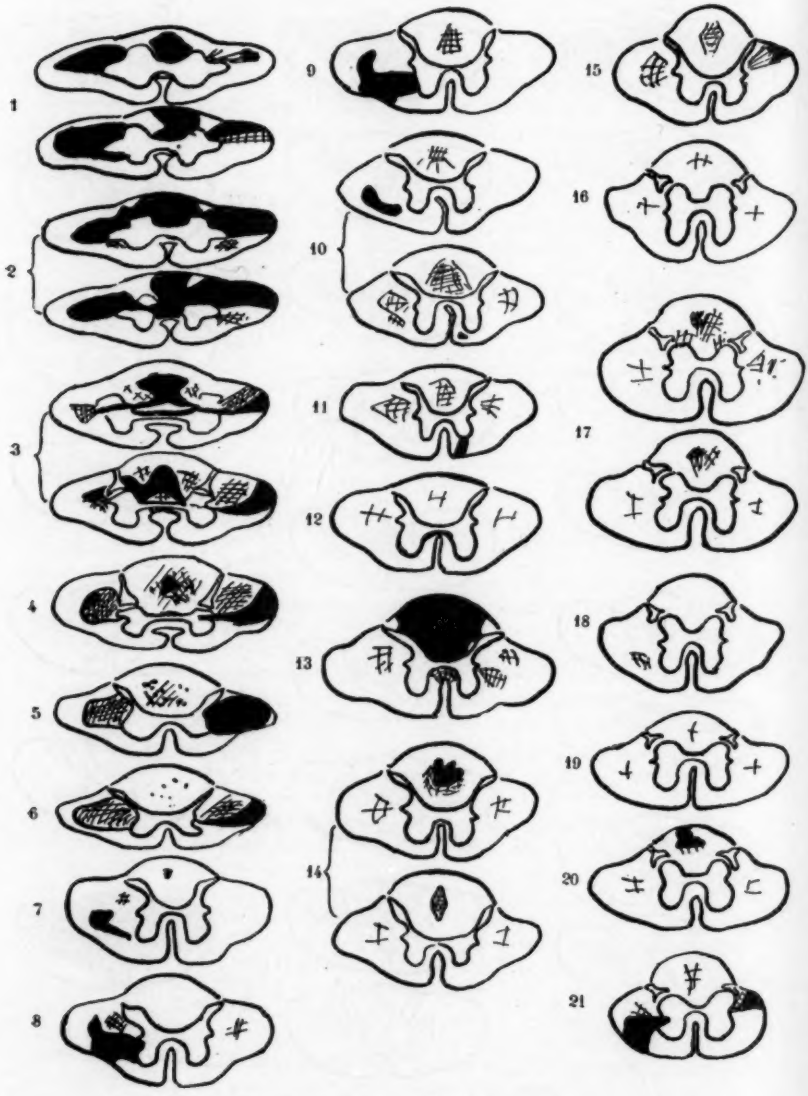


Fig. 8.—Sections of cord in case 4.

The second large plaque of the posterior columns appears in parts 13 and 14. Here the cranial extension is situated in the middle of the white matter of the posterior columns, free from the surface, as well as from the gray matter. At a lower level this plaque gradually involved the entire area of the posterior columns and continued caudally through the center of the posterior columns, along the vertical veins in this region, similar to the plaque previously mentioned. Caudally, in part 14, it continues as a central area of gliosis, which gradually fades away.

As in cases 2 and 3, the progression seems to be effected by slowly developing interfascicular glia.

Parts 17 and 20 show smaller plaques in the posterior columns hardly exceeding the stage of simple gliosis. The plaque of part 17 is the smaller, being only an area of dense perivascular gliosis along the vertical vein of the posterior column. The plaque of part 20 is more extensive, reaching cranially the surface of the cord, surrounding a radial vein and continuing into the substance around a descending branch of this vein. A small perivascular area of gliosis is observed in parts 7 and 8.

The plaques of the lateral columns are situated in the cervical region in a characteristic way as a fanlike area of gliosis with its apex in the horizontal meridian. This fan-shaped area of gliosis on the left side slowly progresses to total demyelination in parts 1 and 2. Cranially, in part 3 the gliosis again progresses after a transient reduction, and a new area of total sclerosis is formed in part 5. Caudal to this it is again reduced. On the right side totally demyelinated plaques appear in parts 1 and 2; then gliotic plaques, which fade away in part 6. The plaques of the left lateral columns show how the total sclerosis first disappears ventrally, and then in the dorsal portion and laterally, as in case 2.

The two plaques of the lateral columns in parts 7, 11 and 21 are remarkable. Larger plaques develop here on the border between the anterior and the lateral column, as may be seen particularly in the plaques of the lumbar region. These plaques also send out extensions into the white matter cranially and caudally at some distance from the surface, while the plaques where they are oldest and the pathologic alterations maximal involve the cord to the surface.

The small plaque of the anterior column seen caudally in part 10 and cranially in part 11 is also characteristic. It begins and ends within the white matter, free of the surface and of the anterior horn except at its maximum extent. In this maximum enlargement the central vein appears as a radial vein.

In the right lateral column in parts 15 and 21 the plaques lie ventrally in the lateral column in the usual way as a fan radiating out from the "axilla." In part 15 the plaque increases within the white matter and reaches the surface at its maximum development.

Paramedian gliosis is scarcely represented. It is seen only caudally in part 13, although in part 2 the central sclerosis has progressed toward the anterior white commissure.

Throughout this cord there is a more or less marked proliferation of the interfascicular glia in the central parts of the posterior and lateral columns. The plaques principally take the T shape. In the maximal and oldest places they may involve the periphery or the gray matter or both. The progression takes place more rapidly cranially and caudally than

laterally and is always limited to the white matter. This is seen most clearly in the small isolated plaques. The large plaques progress along the deep vertical anastomoses, and only at an advanced stage do they involve the lateral portions.

CASE 5.—A man aged 56 had had intermittent symptoms from 1929 to 1940 with progressive involvement until his death in 1942. Autopsy showed multiple sclerosis.

The cord was cut into 20 continuous blocks, beginning in the cervical region; parts 1 to 4 and 11 to 16 were cut in serial sections at a thickness of 7 microns, at intervals of from 60 to 100 microns. From the other blocks only a few pieces were taken for orientation. The plaques in this case were extraordinarily clear, partly because the changes were relatively fresh and partly because they were simple. In general, localization of the changes in this case was similar to that in case 3, but the lesions were fresher. The initial stage of the changes is, therefore, easily reconstructed.

In the posterior columns in the cervical region of the cord there developed an elongated plaque of the characteristic spindle shape, the largest diameter of the spindle corresponding to the oldest changes. The plaque was situated exactly in the center of the posterior column and reached the surface only at its maximum diameter. In cross section it appeared to be situated exactly around the branches of the central veins, the usual single vein being represented in this case by three veins lying closely together. In no place did the plaque exceed the areas drained by these veins.

In serial section the system of arborization of the veins was clearly evident. The deeper portions of the white matter in the anterior, as well as the posterior, columns are drained by long veins, which, after a short course, divide into ascending and descending branches, gradually branching into smaller veins. The radial veins pass to the center of the columns, where they divide, the place of division being approximately at the same level for all veins of equal length.

The outer portions of the columns, and those bordering the gray matter, are drained by short radial veins, which also divide into ascending and descending branches. The long veins anastomose not with the short ones but with the long veins lying above and below.

In the lateral columns of the cervical portion of the cord in this case, a symmetric plaque formation occupied the major portion of the lateral columns in the central region, where the arborization begins. In this case, also, the plaque gradually decreased toward the center of the lateral columns. The vessels arborized in a manner similar to that described.

The remainder of the cord showed constant changes in the form of isolated areas of gliosis in the center of the posterior column and in both lateral columns, i. e., where these columns were widest.

These areas of glioses were not systematically funicular, since their extension and intensity varied, especially in the posterior columns. These gliotic areas were related to the area of drainage of the central veins.

The paramedian zone along the anterior median fissure was almost intact except for parts in the cervical region.

This case provides a useful interpretation of the key to the system of localization of plaques in the more difficult cases 2 and 3. The initial changes are localized in the middle of the posterior and lateral columns,

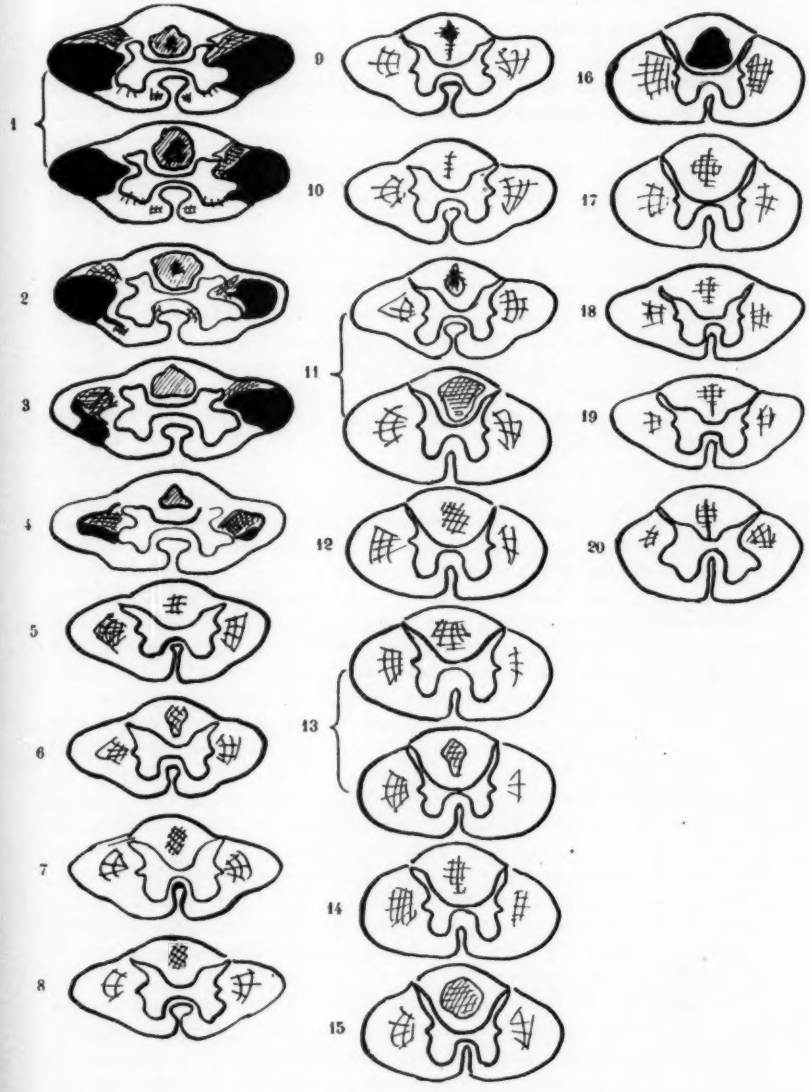


Fig. 9.—Sections of cord in case 5.

apparently at the level where the veins divided into ascending and descending branches. The configuration of plaques and the course of the vessels were easily traced, especially in parts 1 to 4 and 11 to 16. These preparations demonstrate that the plaques are related to venules and their confluence with the veins. The plaques are located by preference in relation to the central vein of the posterior columns, then to one or both lateral veins in the posterior column, later to the more central parts of the gray matter and finally to the superficial parts drained by special wide, short veins. The same principle applies to the lateral columns.

Case 6.—The patient, a woman, apparently first experienced symptoms at the age of 7 years. In 1916 she had two slight attacks. From 1929 until her death in 1943, at the age of 50, there was gradual progression of symptoms.

From the cord three large portions were taken, one from the cervical region, with division into 8 blocks (part 1 to 8); one from the center of the thoracic region, with division into a longitudinal section, and 4 transverse blocks (only parts 11 and 12 are described), and one from the lumbar region, with subdivision into 3 blocks (parts 13, 14 and 15).

The first portion was cut into 22 serial sections; the second portion (parts 11 and 12) into 20 and 22 serial sections, respectively; parts 13 and 14 were cut into 22 serial sections each, and part 15 was cut into 20 serial sections.

It would be impossible to understand the changes seen in this case without knowledge of the alterations of the previous ones. The changes of the first 6 parts, especially, might easily be mistaken for secondary degenerations (Waller). However, this explanation is improbable, for several reasons: First, in this brain were typical sclerotic plaques of classic localization, being periventricular below the lateral ventricles. Therefore the patient had multiple sclerosis. It is known that the secondary systematic degenerations do not occur in multiple sclerosis. The patient might have had another disease with secondary degenerations, but no symptoms of such a disease were noted. Similar pathologic alterations are also seen in other cases of this study.

A more detailed analysis of the alterations described will allay the suspicion of secondary degenerations. The gliosis varied both in form and in intensity, not only in the posterior columns but also in the lateral columns. In the cervical portion of the cord the classic central long area of gliosis is seen extending from part 1, to decrease in parts 2 and 3 and then increase. As in the other cases, the gliosis reached its maximal intensity within the white matter in the central portion of the posterior columns. In parts 4 and 5 gliosis in the remaining portion of the right posterior column was also seen.

The paramedian sclerosis was situated not only along the anterior median fissure itself but also around the base of the fissure; this would not be so in the case of secondary degeneration of the anterior pyramidal tracts.

There was also a great deal of variation in the extent and intensity of gliosis of the lateral columns. Both the intensity and the extent decreased unilaterally in parts 3 and 4 and increased again more caudally. In the lower thoracic region a uniform transverse gliosis was seen, similar to that in other cases at about the same level.

More caudally, at the beginning of the lumbar region, the gliosis decreased in the left lateral column, which gradually became normal. Pathologic alterations were observed again more caudally.

In the last three parts there was almost a hemigliosis. The term, however, is inadequate, as the gliosis, according to the principle of development, was situated on both sides of the midline in the posterior, as well as the anterior, columns, which presented cone-shaped and paramedian areas of gliosis, respectively.

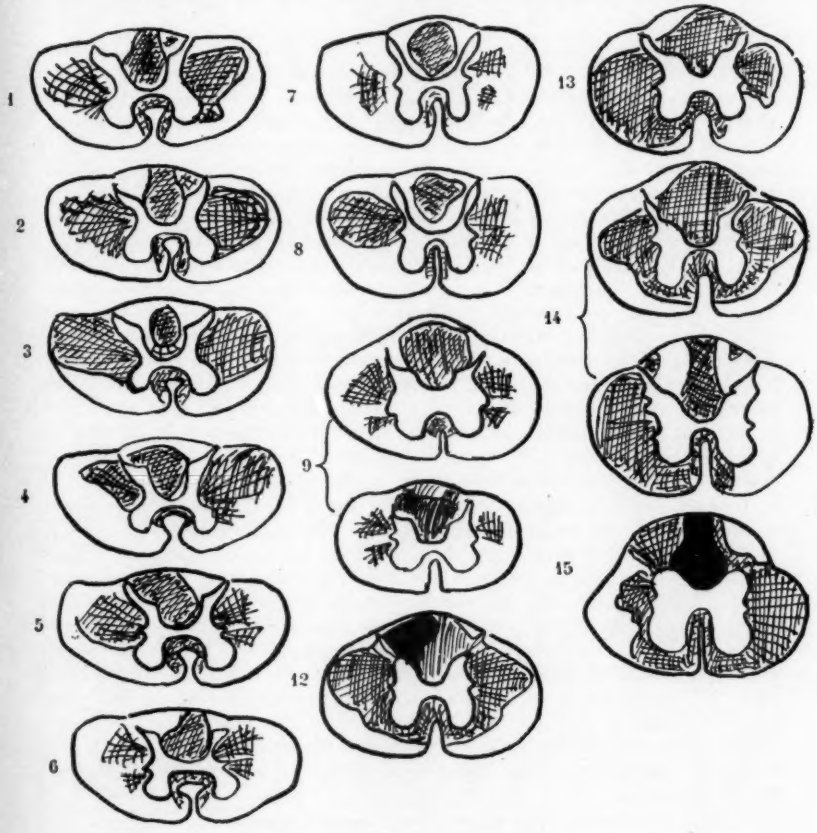


Fig. 10.—Sections of cord in case 6.

Areas of total demyelinations were rare. As mentioned, the glioses reached the greatest intensity within the white substance of the posterior columns in parts 1 and 4. Total demyelination was seen in parts 11, 12 and 15. Part 11 showed intense central gliosis of the posterior columns; part 12, total demyelination of the right lateral column, and part 15, again, gliosis of the center of the posterior columns.

From knowledge of the vascular system, one would conclude that the lateral sclerosis in part 12 corresponds to the drainage territory of

the long lateral vein of the posterior column, a relation evident from the fact that these plaques fade away laterally.

CASE 7.—A man aged 46 showed symptoms of intermittent multiple sclerosis from 1921 to 1940. From 1934 there was gradual progression of symptoms without the appearance of new ones.

The cord was divided into 22 blocks, as follows: cervical region: 4 parts; thoracic region, 10 parts; lumbar region, 8 parts. Each block was cut into about 40 serial sections.

On preliminary investigation the changes in this cord were observed to differ from those in cases 2, 3, 4, 5 and 6 but resembled those in case 1 and in case 8.

On the whole, however, this case presented the same localization of pathologic changes as that in all the other cases, since the changes in the lateral columns followed the usual principle of localization in the posterior columns in the broadest parts and near the "axilla." In the anterior columns the well known paramedian plaques were observed; in the posterior columns the outlines of the pathologic process seemed to vary, but closer analysis of serial sections revealed that these outlines corresponded well to the areas of drainage of the veins, first and foremost, the central vein and both the midline vein and the two lateral veins, as seen in the cervical region. The plaques in the posterior column were inconstantly seen; they were related to the wide veins of the posterior root. In the cervical region, as well as in the entire upper portion of the thoracic region, there was a tendency to dextroposition of plaques, with periodic extension into transverse plaques, which, however, still followed the ruling principles, with sparing of the ventral and lateral portions of the cord. As a result of this dextroposition, the cord was drawn to the right in cross section, with curious configurations, especially of the plaques in the posterior columns. When these were traced in serial section, however, a regular relation to the venous systems was again observed.

It is remarkable to note in these parts how slowly the changes varied in width in correspondence to the predominating vertical course of the veins—in contrast to the analysis of Falkiewicz, who emphasized their variation. In addition, it may be seen that a change in the configuration of the plaque, e. g., the appearance of the so-called plaque rays, can with certainty be related to arborizations of the venous system (compare with sections 32 to 35 of part 2, sections 1 to 12 of part 7 and the changes in the posterior columns throughout part 9). It is of interest to find small isolated plaques. The best example is to be seen in part 1, sections 15 to 23. In the middle of the intact posterior columns some gliosis was seen around the vertical venules. At the point of confluence of these into a larger radial vein, a small, cufflike plaque was seen. This tendency to localization in places where the vessels alter their course from vertical to horizontal was repeated throughout the cord.

It must be mentioned that plaques of the anterior median fissure followed the course of the vein here, either for a longer distance vertically in the fissure or where the vein bent toward the junctions of vessels in the vascular corona.

CASE 8.—A woman aged 50 had symptoms of intermittent course for nine years, with more gradual progression and the appearance of new symptoms during the last eight months of her life. Autopsy revealed multiple sclerosis.

The cord was divided as follows: cervical region, 6 parts; upper third of the thoracic region, 2 continuous parts; lower third of the thoracic region, 1 part, and lumbar region, 1 part. From these serial sections were cut, at intervals of approximately 70 microns.

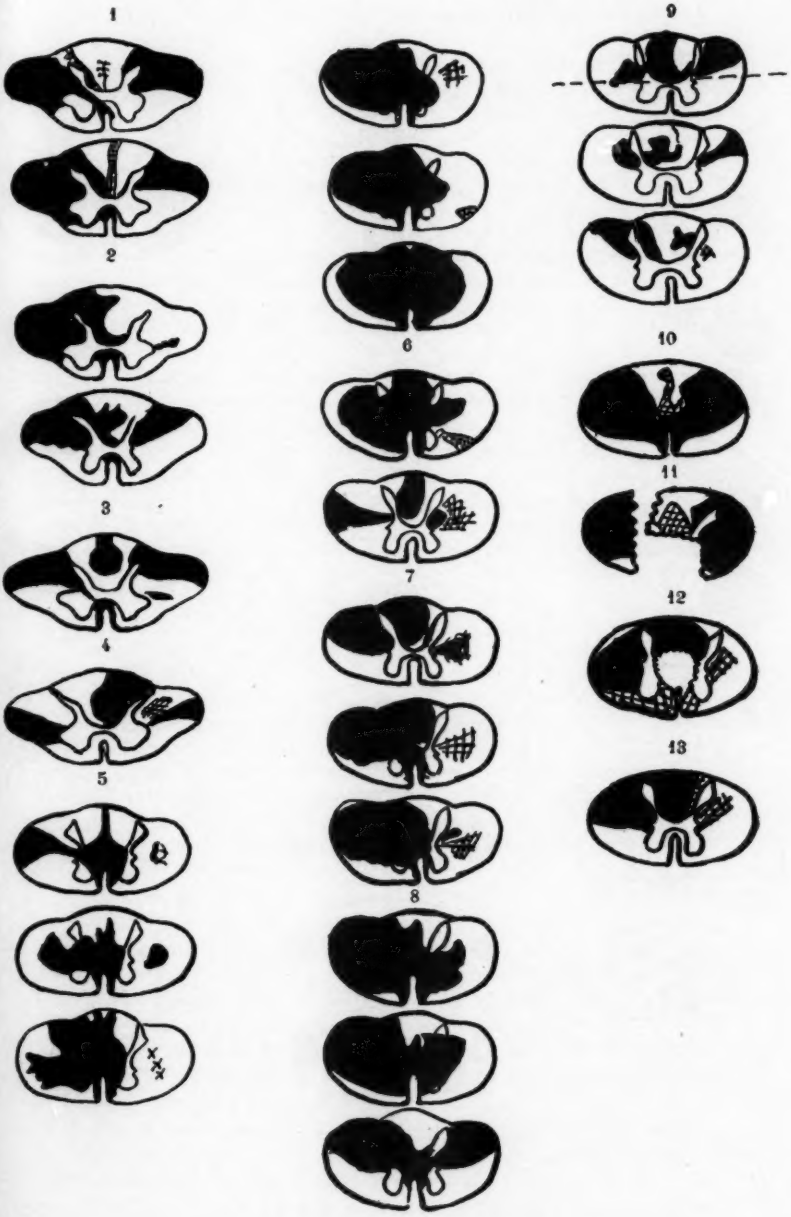


Fig. 11.—Sections of cord in case 7.

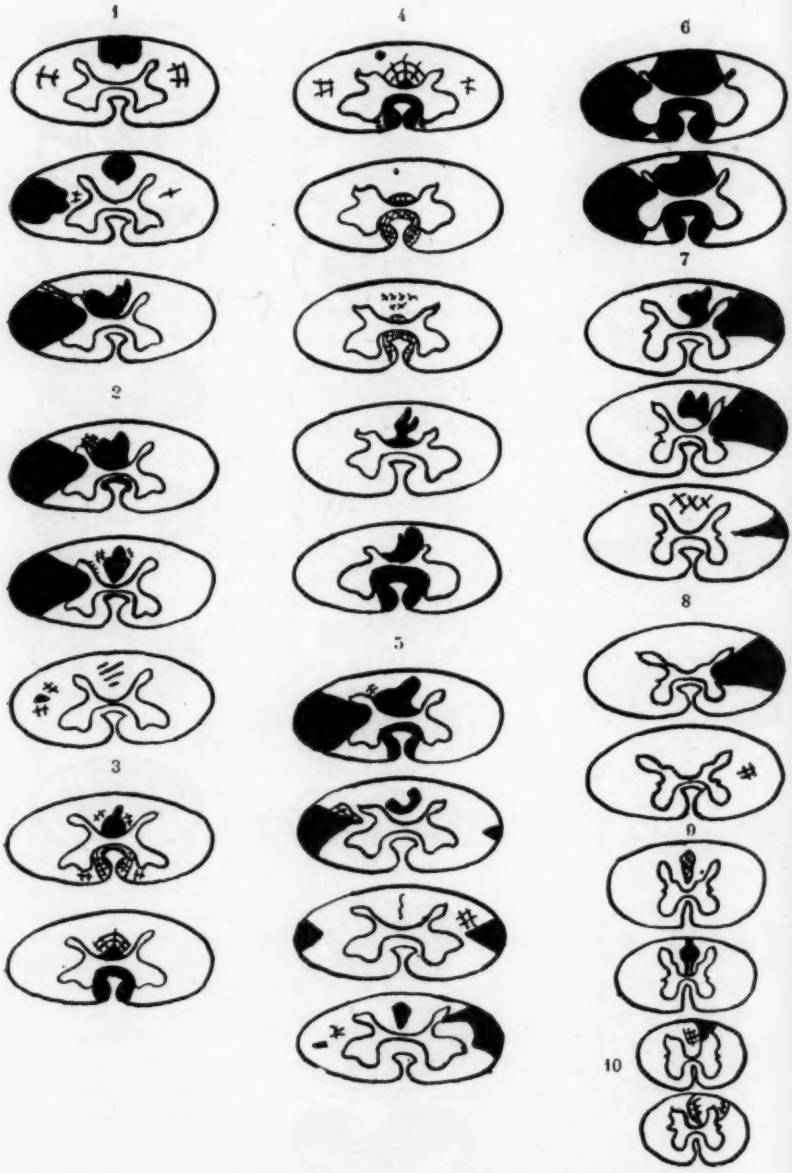


Fig. 12.—Sections of cord in case 8.

This case is similar to cases 1 and 7, although presenting more isolated areas of gliosis than case 7.

In part 1 the process began with a large central plaque, including all three central veins of the posterior columns. Gradually a dextroposition of the changes took place in this portion of the cord, in such a way that the plaque of the posterior column through the posterior commissure on the right side gradually met with a large plaque forming rapidly in the right lateral column. At the same level, the left portion of the central plaque in the posterior column disappeared, and the intensity of the gliosis decreased. The process progressed caudally in part 1 and continued cranially in part 2. At this level it reached the maximum extent, and here the large radial vessels appeared to have a special significance in the posterior column. Caudal to the place of confluence the vessels decreased in width in their vertical course. At the same time the plaque decreased. At first the foremost portion of the right lateral column disappeared, and then the right half of the posterior column, corresponding to the gradual disappearance of the right component of the "triad." Finally, the central portion of the plaque of the posterior column ended as a thin perivascular zone in the middle of the posterior column—clear of the surface, as well as of the gray matter.

In parts 3 and 4 a longish plaque was situated as a very low wedge on the posterior commissure in the midline. The wedge decreased gradually in height throughout part 3 and the first half of part 4, i. e., over an extent of about 150 sections. Over this long stretch the vessels in the plaque ran parallel, and it was observed that the anastomoses in this region were unusually few. In contrast, the normal tissue showed uniformly coursing radial veins, which arborized with great regularity in ascending and descending branches, always at the same level.

In both anterior columns a rather wide, paramedian plaque was seen constantly, symmetrically placed on the two sides of the anterior median fissure. After a transitory reduction, it again increased in width, but still symmetrically. In part 4 a small isolated plaque lay cranially around the right central vein, being widest exactly at the place where the vein turned from its radial to its vertical course. This plaque was completely isolated, and illustrated in miniature the principle of development of the larger plaques. It appeared as a perivascular zone lying symmetrically around a vein, being widest in the place where the vein was also largest, and it was at this junction that the vein turned. It accompanied the descending branches of this vein for a considerable distance through this part, but the localization was constant.

Finally, it may be stated that immediately before and at the point of turning a small fresh thrombus was observed.

In the second half of part 4 a rapid increasing area of gliosis was found somewhat below the surface in the posterior column. Immediately after, radiating veins dipped in from the surface and then turned in a vertical direction. Again, a dense gliosis was seen exactly where the veins turned. This was the peak of a larger focus in the posterior column, which involved even the gray matter and gradually took on a flamelike contour, sending out broad prolongations along the radial course of the veins.

After the rapid decrease of a central plaque in the posterior column a new plaque appeared in this column around the central vein in part 5. Its right branch corresponded with the branching of the central vein.

As in part 1 and 2, a dextroposition of the changes was evident here; the plaque of the right posterior column met through the gray matter a newly formed

extensive plaque in the right lateral column, while a plaque in the left lateral column at the same level was seen to decrease. Along the anterior median fissure a typical paramedian symmetric plaque was formed. At the same level the vein of the anterior median fissure received a great branch from the right side.

Throughout part 6 these changes continued, involving almost the whole of the right half of the cord, as well as symmetric portions of the posterior and anterior columns paramedianly.

In this part it is observed how frequently the veins from the lateral columns ran centrally into the gray matter, not solely toward the periphery.

Part 7 shows sinistroposition of the degenerative changes according to the principle already described. Here, also, a large plaque in the middle of the posterior column united with a corresponding plaque around the vein of the posterior left column and followed the left branch of the central vein down into a large plaque of the left lateral column. The reduction of the plaque followed the usual patterns, fading away in both columns within the white matter around the decreasing vertical venous branches. In part 8 the lateral plaque was again larger but soon decreased according to the principles described.

Part 9 shows a central plaque of the posterior column around branches of the vertical vein. In part 10 is seen a "negative" of the usual changes, the most diseased portions of the posterior column corresponding to the pattern of the lateral vein in the left lateral column. The localization of the central changes is determined by an obliquely running vein. The changes increase and localize along the vein of the posterior column, and the venous territory near the posterior commissure, a "negative" of the vascular pattern of the plaque in parts 3 and 4.

The changes in this cord were situated around parallel vertically running veins and venules, uniting into larger common trunks. Their maximum extent was identical with the maximum venous diameter, i.e., the maximum diameter of a plaque occurred where the veins turned from a vertical to a radial course, while the plaques decreased with the decrease in the size of the vessels.

Anastomoses between the individual veins were rare and insignificant. Longitudinally, however, the veins anastomosed with corresponding veins above and below. This applies especially to the central veins in the posterior columns and in the anterior median fissure. Consequently, the length of the plaques might be considerable as compared with the width.

During the development of a plaque a certain uniformity in intensity and rhythm was observed in a cross section, producing the alternate dextroposition and sinistroposition of the plaques.

## SUMMARY

On the basis of present knowledge of the vascular pattern of the spinal cord, the topographic distribution of plaques may easily be related to the spinal veins and their drainage territories.

In 8 cases of multiple sclerosis serial sections were made of the spinal cord. In 5 cases the cord was almost fully sectioned in order

to make possible a complete survey of the changes, while in 3 cases continuous parts were taken for preparation.

The terms "changes" and "alterations" have been used purposely to include gliosis, as well as plaques in the classic sense.

In all 8 cases changes were localized to the posterior and lateral columns, within closely defined territories and fairly constant in shape. In cases in which the anterior columns were included the localization and shape were also constant. In the posterior columns the place of predilection was the central area, as the changes were situated symmetrically on the two sides of the midline; consequently, the plaques of the posterior columns were situated usually in pairs. Unilateral plaques were rare and were always rather small here.

In the lateral columns the widest dorsal portions were constantly attacked, involving as a rule the pyramidal tracts. The plaques usually exceeded the territory of these tracts, especially medially, and involved the space termed the "axilla," i.e., the space just lateral to the angle between the ventral and the dorsal horn.

The changes frequently continued into the adjacent lateral parts of the posterior columns, along the posterior horn or medially into the gray matter on either side of the central canal. Variations were seen, especially in the lumbar region; in principle, however, as in the posterior columns, the place of preference was where the white matter was broadest, in other words, dorsally in the lateral columns and centrally in the posterior columns.

In the anterior columns the place of preference was definitely the region along the anterior median fissure. The changes were almost always symmetric, as in the posterior columns. The area affected usually included the anterior pyramidal tracts but often considerably exceeded the tracts, especially centrally around the base of the anterior median fissure, i.e., into the anterior white commissure, in communication with central plaques.

With regard to shape and extent, certain common features were also observed. Cases of chronic multiple sclerosis are difficult to analyze, as the changes are more extensive. In principle they do not differ, however, from the cases of the acute disease. By analysis of the latter it is possible to obtain a full survey of their shape and extent. The system is only sketched here, but details are given in the summary of the individual cases.

In figure 13, *C* and *D* illustrate the system schematically. At the level of the maximum extent of a plaque in the posterior column, the shape on cross section usually resembles a cone or a wedge, with the base directed centrally and the apex pointing toward the periphery. Above or below the level of maximum development the cross

section of the plaque is usually more oval and is placed centrally in the posterior column. The shape is also fairly uniform both cranial and caudal to the maximum level, the size decreasing with the caliber of the vessels.

There is good correlation between the form of the plaques and the shape of the venous pattern, as this was described by Herren and Alexander (fig. 6). Mager (1900-1901), in his report on cases of

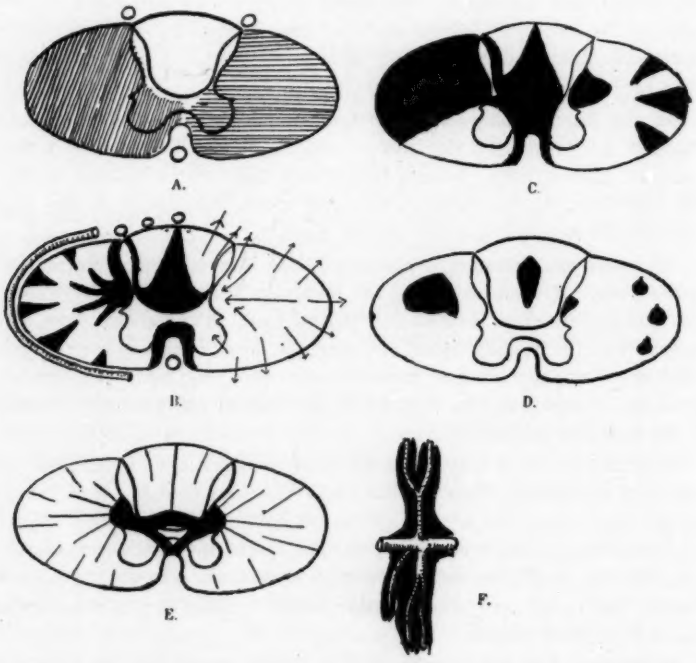


Fig. 13.—Topographic distribution of spinal vessel territories and of spinal plaques. *A* shows arterial supply; *B*, venous territories; *C* and *D*, topography of plaques at two levels; *E*, glial architecture; *F*, isolated plaque formation in longitudinal section.

acute myelitis, described fresh myelitic foci in a similar schematic form, but in a different pattern.

Plaques in the posterior column in their clearest form were observed in case 1, parts 1, 3, 4, 6, 7, 8, 9, 12, 19 and 20. In the following preparations the centrally placed cranial and caudal ramifications were also observed: case 4, parts 1 to 20, corresponding to figure 13 *B*; case 8, parts 1, 2, 5 and 6 and caudally, parts 4 and 9; case 5, parts 1

to 4, 9 to 12 and 13 and 14; case 7, parts 1, 3 and 9 and caudally, parts 5, 11 and 12; case 3, parts 1 to 4 and 5 to 18; case 2, parts 7, 12, 14, 15, 18, 21 and others.

In other places the contours of the plaques were more irregular, since the remaining parts of the posterior columns were also pathologically changed. These lateral plaques were always smaller than the central ones. The shape of the small plaques was the same as that of the large ones, the maximal diameter corresponding to the greater radial veins. Such isolated lateral plaques were seen in case 3, and in case 1, parts 1, 2, 15, 16 and 19. Confluence between a central and an individual plaque in the lateral posterior column was observed in case 1, parts 9, 19 and 20; in case 8, parts 4, 7 and 10; in case 7, parts 4, 6, 7 and 9; in case 2, parts 8, 27, 32 and 34 and in case 6, parts 4, 5, 14 and 15.

The fan shape was with few exceptions the prototype of the plaques in the lateral column. Some plaques appeared rounded (e. g., case 1, part 2, caudally). The size of the fan varied. The plaques were large usually and included most of the columns, and as a rule the dorsal two thirds to three fourths was involved. In their maximum the plaques reached the surface, as well as the gray matter. Cranially and caudally to this maximum diameter the plaques withdrew into the white matter, in accordance with the usual pattern (fig. 13, *F*): case 1, parts 4, 5, 6, 12, 13, 17 and 19; case 5, parts 7, 10, 15 and 21; case 4, parts 3 and 4; case 7, parts 8 and 9; case 2, parts 8, 10, 11, 12, 14 to 17 and 22 to 25; case 8, parts 1, 2 and 8; case 3, parts 1 to 12; case 6, parts 4 to 5, and others. The picture was clearest in the cervical region in case 4.

Further consideration is given to the small independent, isolated perivascular plaques. On first impression they bore a striking resemblance to the perivascular degenerations seen in postinfectious acute encephalomyelitis. They occurred in large numbers throughout the entire cord in case 1 and were seen in the zones of progression. They were also to be seen, independent of these larger plaques, as isolated little plaques in normal tissue. Such a small plaque has been described in detail in part 4 in case 8. In case 5 a small plaque was seen in the right posterior column and throughout parts 10 and 11, and another small plaque was observed in part 17. Other examples of such isolated plaques were found in case 4, part 9, in the posterior column, and another in part 11; in case 7, part 6, in the left lateral column, and part 5, in the same column, and, farther on in part 1, in the left posterior column, and, finally, in case 1, part 19 (figs 1 to 4).

The so-called plaque rays were also frequent, where the plaques sent out radiating prolongations along the vessels, forming perivascular sleeves.

In the anterior columns the plaques usually consisted of symmetric bands on each side of the anterior median fissure. The bands varied in width but were always of approximately equal width on the two sides of the fissure. Exceptions were observed only where these plaques fused with the rare plaques of the lateral portions of the anterior columns. Paramedian plaques were seen in all cases except in case 4, in which the process had not yet begun in the anterior columns. The length of these plaques was variable. The longest ones were seen in the thoracic region of the cord, where the vein of the anterior median fissure runs in an almost perpendicular course.

A continuation of this plaque could often be traced into the gray matter, corresponding to the branching of the vein of the anterior median fissure in the paramedian venous system. This is illustrated in case 1, part 2, in which the paramedian plaque followed the vein through its course from the center to the periphery. In part 18 of the same case the plaque started as a simple central plaque around the central canal, gradually fading away along the anterior median fissure. Centrally in part 19 this process began again, but in the opposite direction, toward the center.

Central plaques were formed by progression of plaques either from the lateral columns (case 1, parts 1, 2, 7, 8, 13, 14, 17, 18, and 20; case 7, parts 1, 8 and 11), from the posterior columns (case 1, part 3; case 8, parts 3, 4, 5 and 6) or from the posterior and lateral columns (case 1, parts 4, 9-12; case 8, parts 5 and 6; case 7, parts 1-2, 8-7, 6-5; case 3, part 22, and case 5, part 2).

The larger plaques were apparently the result chiefly of fusion of many small perivenous plaques. Where plaques of the lateral columns communicated with those of the posterior or anterior columns, fusion always took place along larger venous trunks, usually in the pericentral network.

In the chronic progressive cases the changes were often so extensive that almost the entire cross section of the white matter was involved. As demonstrated in the figures, analysis is possible in these cases. It is remarkable that an intact zone around the entire periphery of these transverse plaques was often seen (case 2, parts 23 and 24; case 3, part 1, and case 6, parts 1, 2 and 3). This illustrates how the shape of plaques is determined by the branching of vessels.

When the spinal cord is considered as a unit, it is apparent that the central portions of the posterior columns are involved in all cases without exception, with the development of long plaques, which may extend throughout most of the cord, with variable extent and intensity. In the chronic progressive cases 2 and 3, scarcely any disseminated

pathologic changes were apparent in the longitudinal axis, but the entire cord was diffusely involved in this area. In the other cases some dissemination was left. The next region to be involved after the central region is one of the lateral veins in the posterior columns in continuity with the territory of the central vein. The central portions corresponding to the posterior commissure are attacked next, and the superficial layers are involved last.

In a similar way the changes progress in the lateral columns, where the central areas are involved first and the peripheral superficial areas last.

In each case, and in each plaque, the progression thus takes place within the central portions of the white matter. Judging from the places where isolated small plaques have been found, the progression usually begins in the place where the radial vein divides into ascending and descending branches. At this site the oldest plaques reach their maximum development.

The progression of plaques in the longitudinal direction, while in the transverse plane they seem stationary, is probably due to the fact that the veins anastomose in the longitudinal direction but hardly ever in the transverse direction. Since the plaque corresponds to the branching of the veins, the absence of horizontal anastomoses of these veins may be traced in the form of the plaques. In other words, the veins form neutral, isolated drainage systems in the transverse plane within the pattern described.

It is further observed that the plaque always originates where the white matter is broadest, i. e., centrally in the posterior columns and dorsally or centrally in the lateral columns, according to the contours of the cord. The superficial zones are involved last.

This fact may be explained by the fact that the drainage is inadequate in the central portions of the white matter and better in the more superficial areas, where numerous short venules anastomose with the venous network on the surface of the cord. Centrally there are anastomoses with the network of the gray matter, but only in the ventral third of the lateral columns, the remaining areas being drained through the veins in the "axilla." In other words, if the spinal cord is involved by a vascular disturbance, the first areas to be affected will be the ones with the least drainage. These are the regions where the initial changes are localized.

According to the findings described in this study, a venous territory must be defined as the territory lying around a vein and its branches, and it is evident that plaques in all details correspond to these venous territories.

## CONCLUSION

Spinal plaques have a predilection for a distinct localization. In the posterior columns they always lie in the center; in the lateral columns, in the center and posterior two thirds, and in the ventral columns, symmetrically on both sides of the anterior median fissure.

The changes begin in the center of the columns, where the diameter of the white matter is greatest. These changes appear around the radial veins. The plaques are of extraordinary length but small in diameter. As the plaque grows, it first spreads toward the central gray matter, where fusion of plaques from the posterior, lateral and ventral columns takes place. Finally, the lesion reaches the surface of the spinal cord. This mode of progression may be explained by differences in the venous drainage.

# HISTAMINE THERAPY IN ACUTE ISCHEMIA OF THE BRAIN

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EVALUATION of therapy in acute ischemia of the brain caused by arterial thrombosis, embolism and vascular insufficiency is sometimes difficult, since the incidence of spontaneous improvement can be rather high.[1] When a type of therapy produces consistent improvement, reduces the mortality and is readily available, simple to administer and safe to use, it merits consideration as a valuable addition to the therapeutic armamentarium. In my experience, such is the status of histamine therapy in acute ischemia of the brain. This preliminary report is made to stimulate further the evaluation of histamine therapy in this field.

Whether the mechanism of ischemia of the brain is an intravascular thrombosis, a sudden vascular obstruction with reflex arterial spasm or a lowered blood pressure in a sclerotic but patent artery, the areas supplied by these vessels are in a state of anoxia.[2] Unless the original or collateral circulation is established early enough, the nerve cells and fiber tracts in the ischemic areas will degenerate and die. The dissolution of clots is not feasible, but the prevention of further thrombosis can be attempted through heparin and dicumarol.[1] Arterial spasm can be relieved by sympathetic ganglion injection[1] or administration of papaverine hydrochloride.[3] Collapse of the blood pressure can be remedied by intravenous administration of fluids. Saturating the blood with oxygen will assist in overcoming the anoxia, provided the blood can reach the ischemic areas.

Unfortunately, these measures are not in widespread use. The anticoagulants require special laboratory facilities and clinical skill in their

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From the Neuropsychiatric Service, Birmingham Veterans Administration Hospital.

Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

1. Gilbert, N. C., and de Takats, G.: Emergency Treatment of Apoplexy, J. A. M. A. **136**:659 (March 6) 1948.

2. Aring, C. D.: Vascular Diseases of the Nervous System, Brain **68**:28 (March) 1945.

3. Russek, H. I., and Zohman, B. I.: Papaverine in Cerebral Angiospasm (Vascular Encephalopathy), J. A. M. A. **136**:931 (April 3) 1948.

administration. The risk of adding hemorrhage to the lesion deters the cautious. The art of injection of the stellate ganglia has been acquired by only a few. The therapy in these cases has too frequently been limited to intravenous administration of fluids and administration of oxygen at best and mere rest in bed at the least. The first days of the illness, when vasodilation therapy would bring the best results, are seldom utilized by physicians in the receiving hospitals or on the medical wards of a general hospital. By the time the patient reaches a neurologist, the most important hours and days have frequently slipped by and too often irreversible changes have occurred.

The problem was considered to be best approached through an attempt to establish collateral circulation. An increase of the capillary beds of the involved areas of the brain was deemed the goal if the cells and tracts in the reversible stages were to be salvaged. Despite the vasodilatation there should be no drop in blood pressure, a stipulation seemingly paradoxic.

Yet the substance that had demonstrated just these desired properties was histamine. Detailed investigations of the effects of histamine in man were reported in 1932 by Weiss, Robb and Ellis.[4] They observed that when histamine phosphate was given by slow intravenous infusion, a widespread dilation of the arterioles, capillaries and venules of the brain and skin occurred without any change in the arterial or venous pressures and without any distress to the patient. This was in striking contrast to the depression of the blood pressure in animals [5] and in man [6] by other technics of administering histamine. An increase in the cardiac output and a lack of vasodilatation in the viscera are considered to explain the integrity of the blood pressures.[4]

The speed of administration of histamine is the determining factor in its therapeutic application to man. The sudden injection of 0.1 mg. of histamine phosphate can produce an intense reaction, whereas 10 to 20 mg. can be tolerated without toxic effects if given in a slow intravenous infusion over a period of one hour.[4] The cerebral vessels were noted to be more sensitive to histamine than even the facial vessels. The minimal effectual dosage to produce cerebral vasodilatation ranged from 0.006 to 0.02 mg. of histamine phosphate a minute.[4] The facial flush, however, is a very convenient index of vasodilatation during therapy.

4. Weiss, S.; Robb, G. P., and Ellis, L.: The Systemic Effects of Histamine in Man with Special Reference to the Responses of the Cardiovascular System, Arch. Int. Med. **49**:360 (March) 1932.

5. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Baltimore, Williams & Wilkins Company, 1939, p. 477. Weiss, Robb and Ellis.[4]

6. Taylor, J. H.: Histamine Treatment of Cerebral Arteriosclerosis, Dis. Nerv. System **8**:154 (May) 1947.

The fate of histamine in the body is not definitely known. It is probably inactivated by an enzyme, histaminase, which is found in many tissues and organs, particularly the intestines and kidneys.[7] The effect of histamine infused at a rate of 0.02 mg. a minute is not detectable ten minutes after the discontinuation of the infusion.[4]

Fortunately, histamine was no newcomer to the field of therapeutic vasodilation. I had given hundreds of injections of histamine in the treatment of multiple sclerosis without any untoward reactions. The dosage used in those cases had produced a vasodilatation that could be readily observed in the skin. The preparations consisted of 2.75 mg. of histamine diphosphate in 500 cc. of fluid given in a period of two hours. This amount of histamine diphosphate is equal to 1 mg. of histamine base. In the usual administration just described, the patient received 0.023 mg. of histamine diphosphate a minute, an excellent approximation of the largest minimal dose that produced cerebral vasodilatation, i. e., 0.02 mg. per minute. This amount was also well within the range of dosage that had been found to produce no change in the blood pressure, the upper limit being 0.08 mg. of histamine phosphate a minute.[4]

The same regimen of histamine administration was applied in cases of acute ischemia of the brain, i. e., 2.75 mg. of histamine diphosphate in 500 cc. of isotonic fluid given intravenously in a period of two hours. People with vascular lesions were found to tolerate histamine as well as those with multiple sclerosis had done. The drug was easily administered; the infusion could be readily adjusted or terminated, and no special skills or laboratory procedures were required. Ampules containing 2.75 mg. of histamine diphosphate are conveniently available.[8] Isotonic saline, 5 per cent dextrose or any similar solution can be used as the vehicle. The histamine solution was given once or twice daily for periods of four to twenty-one days, depending on the progress of the case.[9]

As adjuncts to the histamine therapy, most of the patients were given 50 to 100 mg. of nicotinic acid by mouth three or four times a day to secure additional vasodilatation. Nicotinic acid has been used routinely by me for prophylactic and therapeutic vasodilatation in

7. Cushny, A. R.: Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1947, p. 522.

8. Abbott Laboratories supply 1 cc. ampules containing 2.75 mg. of histamine diphosphate (1 mg. of histamine base). Other preparations can be used, so long as the total amount of histamine diphosphate added to the 500 cc. of fluid is 2.75 mg. The diphosphate, acid phosphate and phosphate salts are identical. The formula is always 2.75 mg. of the histamine salt equals 1 mg. of the histamine base.

9. So far as can be ascertained, this is the first published report of the application of the slow intravenous infusion of histamine in cases of acute cerebral ischemia.

vascular diseases of the nervous system. It is the best cerebral vasodilator available for oral administration, possessing the very desirable property of not affecting the blood pressure during the effective vasodilatation.[2] In some cases heparin, dicumarol,* papaverine and oxygen were utilized in the therapeutic attack on the ischemia of the brain.

It is also very important to prevent the bronchopneumonia that contributes heavily to the mortality in these cases.[10] Early return to activity, proper pulmonary ventilation and drainage and prophylactic chemotherapy if the response is not satisfactory are invaluable measures in the therapeutic regimen.

As for the contraindications to histamine therapy, the application of vasodilator substances in cases of hemorrhage is undesirable because the vasodilatation might cause a recurrence of the bleeding. Another

TABLE 1.—*Symptoms and Signs of Value in Differentiation of Cerebral Hemorrhage and Cerebral Thrombosis*

| Symptom or Sign | Hemorrhage | Thrombosis |
|---|---|---|
| Spinal fluid pressure over 400 | (20 per cent of cases) | (none) |
| Grossly bloody fluid | 49 | 1 |
| Spinal fluid pressure over 300 | 14 | 1 |
| Severe headache | 10 | 1 |
| Progression of signs | 9 | 1 |
| Stiffness of the neck | 8 | 1 |
| Vomiting | 8 | 1 |
| Cheyne-Stokes respiration | 5 | 1 |
| White blood count over 12,000 | 5 | 1 |
| Clear spinal fluid | 1 | 4 |
| Quadriplegia | 4 | 1 |
| Coma | 2 | 1 |

reason is that during infusion of histamine the spinal fluid pressure is increased, an undesirable occurrence when the intracranial contents are already under increased pressure from the hemorrhage. Familiarity with the classic article of Aring and Merritt[10a] on the differentiation between hemorrhage and thrombosis is an inestimable asset to anyone treating vascular lesions of the brain. Their study demonstrated that the presence or absence of an elevated blood pressure or peripheral arteriosclerosis and whether the onset of symptoms occurred during activity or at rest are of little practical value in the differentiation, since they occur with equal frequency in hemorrhage and thrombosis. The symptoms and signs that are of value are listed in table 1. The relative frequencies are given as ratios, based on the observations of Aring and Merritt[10a]

Histamine should be used cautiously in cases of asthma since some asthmatic patients show an idiosyncrasy to the drug.[4] Patients with

10. (*a*) Aring, C. D., and Merritt, H. H.: Differential Diagnosis Between Cerebral Hemorrhage and Cerebral Thrombosis, Arch. Int. Med. **56**:435 (Sept.) 1935. (*b*) Gilbert and de Takats.[1]

cardiac decompensation do not show any increased sensitivity to histamine, even though circulation may be three or four times slower than normal.[4]

## RESULTS

The first 25 cases of acute ischemia of the brain in which the slow intravenous infusion of histamine was used form the basis of this report. There has been 1 death, due to uremia and heart failure. This man had recovered with histamine therapy from two episodes of hemiplegia, on the left and on the right, three months and two weeks before his death.

The patients have been classified according to the response during the actual period of histamine therapy and have been grouped as follows:

Group I: 20 patients—definite improvement in all affected fields to the extent that appreciable function had returned.

Group II: 3 patients—definite improvement in some fields, but none in others, as amelerioration of sensory symptoms but not motor recovery.

Group III: 2 patients—no apparent change.

In the follow-up period of two to twelve months, the patients of group I continued to show resolution of their findings. Patients of groups II and III have been stationary except 1 (case 5), who showed marked motor and sensory improvement in the third month.

The distribution of results in relation to time of institution of histamine therapy is as follows:

TABLE 2.—*Results of Histamine Therapy in Relation to Time of Institution*

| | Number of Cases | | | |
|---|---|---|---|---|
| Day | Total | Group I | Group II | Group III |
| 1..... | 11 | 9 | 1 | 1 |
| 2..... | 4 | 4 | 0 | 0 |
| 3..... | 8 | 6 | 2 | 0 |
| 5..... | 1 | 1 | 0 | 0 |
| 7..... | 1 | 0 | 0 | 1 |

I have gained the impression that when thrombosis of a major artery occurs recovery will be minimal, even with vasodilator therapy. Fortunately, most cases of clinical "thrombosis" are, in reality, instances of cerebral ischemia due to vascular insufficiency in regions supplied by sclerotic but patent arteries.[2] In these cases of cerebral or brain stem ischemia the most gratifying responses to histamine therapy are shown.

Although the series is still small, the trend observed is significant, especially if the usual course of cerebral thormbosis is considered. Aring and Merritt in 1935 reported that of 96 patients with verified thromboses, 64 per cent had survived only two weeks and 86 per cent two months after onset of symptoms.[10a] Gilbert and de Takats in 1948 gave an analysis of 53 cases of thrombosis.[1] Twenty-four per cent

of the patients had died of the cerebral lesion or bronchopneumonia within four weeks. Of the surviving patients, 38 per cent (of the entire series) had improved and 38 per cent had not changed.

Gilbert and de Takats,[1] in another series of 12 cases of thromboses, injected procaine hydrochloride into the stellate ganglion to secure improvement in the cerebral circulation. Three of these patients died, 2 of bronchopneumonia and 1 of coronary thrombosis within five to eighteen days of the onset of symptoms. Of the surviving 9 patients, 8 were considered to have improved.

Thus a definite trend toward lower mortality and more frequent recovery is observed in cases of cerebral ischemia treated by vasodilators whether this vasodilatation is accomplished by paralyzing the sympathetic nerve supply to the cerebral vessels or through active dilation by the chemicals histamine and nicotinic acid.

The present procedure in use is to exclude from histamine treatment a patient suspected of having a brain tumor if the history is suggestive and if the intracranial pressure is found elevated by either manometric determinations or changes in the fundi. Spinal puncture is done if the fundi show no papilledema. If the fluid is grossly bloody or the pressure over 300 mm. of water, histamine is not given. When the fluid is clear and the pressure below 200 mm., administration of histamine is begun. Four hours of continuous vasodilation is given at the first infusion, i. e., 1,000 cc. of the histamine solution. After this initial infusion, 500 cc. is given three times a day until improvement has been maintained several days. Then the infusions are decreased to two and one a day for a week. Patients who show little change receive infusions of histamine three times a day for at least two weeks. Nicotinic acid, 100 mg. four times a day, is administered orally between infusions to maintain vasodilatation. If the spinal fluid is clear but the pressure is between 200 and 300 mm., histamine is given cautiously if clinical evaluation is against an encapsulated hemorrhage and in favor of cerebral ischemia with edema.

The following case reports illustrate the responses of ischemia of the brain to histamine and nicotinic acid therapy. The first 4 cases are examples of cases of group I, and case 5, of group III.

## REPORT OF CASES

CASE 1.—*Old thrombosis of the left internal auditory artery; recent thrombosis of midbrain branches of the left superior cerebellar artery.*

*Symptoms.*—In May 1948 a 60 year old barber while working had experienced a sudden onset of deafness, roaring and ringing in the left ear accompanied with severe vertigo. The vertigo subsided in several weeks. In July he noted a gradual onset and progression over a four week period of numbness, first in the face and then in the arm and leg on the right side. During this period he also had intermittent attacks of hiccup.

*Observations.*—In August he could not walk tandem or balance on one leg. His coordination was poor in the right arm. All sensation except light touch was diminished on the whole right side, particularly in the hand. Bone and air conduction of sound was not perceived on the left, and there was no response on the left to the cold caloric test. A horizontal nystagmus in direction of gaze was present, greater on looking to the right. Hiccups occurred in frequent bouts. The physical examination otherwise revealed normal conditions. The spinal fluid, roentgenograms of the skull, including special views of the petrous bones, and routine examinations of the blood and urine showed no abnormalities.

*Treatment.*—For one week the patient received 100 mg. of nicotinic acid three times daily. He then had an episode of nausea, vomiting, and vertigo and an increase in the numbness in his leg. Histamine therapy was then instituted, one infusion a day. Examination on the fifth day of histamine therapy showed definite improvement of the ataxia and sensory deficit. He hiccuped much less frequently. In addition, a Babinski sign on the right and vertical nystagmus were noted. Histamine therapy was discontinued after eight days. Administration of nicotinic acid, 50 mg. four times a day, was continued. One month later he could walk tandem and balance on one leg. The positive Babinski sign was still present on the right. Sensation was then normal in the lower limb, but the diminution of all modalities was still noted in the upper limb. The patient could now hear a 128 and a 1024 tuning fork in the left ear through air and bone. The hiccup had disappeared. The electroencephalogram was reported as normal at this time. He was discharged as markedly improved and was still well at the time of writing, four months later.

CASE 2.—*Thrombosis of diencephalic branches of the left posterior cerebral artery.*

*Symptoms.*—A 45 year old man was in the hospital for a discogenic syndrome. Early one evening he got out of bed and fell to the floor when his right leg gave away because of severe weakness. He became disoriented, complained of severe headache, had auditory and visual hallucinations and then stopped talking.

*Observations.*—One hour after the fall he was observed to be unable to speak or understand spoken speech or even to write his own name. A flaccid hemiplegia was evident on the right, and there was no response to painful stimuli on the right side of the body. The spinal fluid pressure and chemistry were normal, as they had also been three weeks before. The next morning he complained of pains in the whole right side of the body. There was no evidence of aphasia then. Moderate weakness of the right limbs and lower facial muscles was present. All sensation was diminished on the right but not to complete loss of any modality. The Babinski sign was positive on the right, and the left pupil was 2 mm. larger on the left. The right ankle jerk could not be elicited, a finding antedating the hemiplegia.

*Treatment.*—Intravenous infusion of histamine was begun on the morning after the onset of symptoms, and treatment was given once a day for eleven days. During this time the patient made rapid improvement, becoming ambulatory and being able to use his right hand for writing, smoking, shaving and dressing, although the power had not returned to normal. At the end of histamine therapy he could perform rapid alternating movements on the right as well as on the left. The face, trunk and limbs on the right were analgesic, but modalities other than pain were perceived although less readily than on the left. It was interesting that this patient had chronic asthma but actually had fewer episodes of asthma during the period

of histamine therapy than before. Nicotinic acid, 50 mg. four times a day, was given during and after histamine therapy. The patient was discharged as markedly improved six weeks after the onset of symptoms.

CASE 3.—*Ischemia of tegmental branches of the left superior cerebellar artery.*

*Symptoms.*—A 48 year old woman during activity experienced the sudden onset of dizziness, nausea, vomiting and instability of gait. Five hours later she began to have severe retro-orbital pains whenever she moved her eyes or head.

*Observations.*—On the second day of her illness she had a mild ataxia of all the limbs, more pronounced on the left; a diminution of all sensation on the whole right side, and a horizontal nystagmus to the left on lateral gaze to either side. The physical examination otherwise showed no abnormalities. Studies of the spinal fluid, roentgenograms of the skull and routine examinations of the urine and blood, including serologic tests, disclosed no abnormalities. By the third day of the illness, the ataxia of the limbs was marked, especially in the arms. The sensory system was then intact. A horizontal nystagmus in the direction of gaze was easily elicited. The patient complained of severe retro-orbital pains whenever the eyes or head were moved. Her hearing was normal, and she had no tinnitus.

*Treatment.*—Infusions of histamine were begun on the third day of the illness. After the first injection, the ataxia almost disappeared, and the patient had no further nausea or vomiting. Histamine was given for four days, at the end of which time only a fine nystagmus to the left on left lateral gaze and a moderate hypersensitivity of the vestibular system remained. Dicumarol® therapy had been begun with the histamine and exerted an effect during the last two days of the histamine therapy. Nicotinic acid, 100 mg. four times a day, was given daily from the third day of the illness. Examination one week later disclosed only a slight nystagmus and a mild hypersensitivity of the vestibular system. Two weeks later the patient was without symptoms and signs and was discharged as recovered, less than one month after onset of her illness.

CASE 4.—*Thrombosis of capsular branches of the right middle cerebral artery.*

*Symptoms.*—A 71 year old actively working rancher had had episodes of blurring of vision and dizzy spells for four months. One morning his wife found him comatose near his bed.

*Observations.*—One day later the patient was still semicomatose and showed a flaccid weakness of the left side of the body, including the face. He responded to painful stimuli equally well on the two sides of the body. The Babinski reflex was positive on the left. The physical examination otherwise did not disclose abnormalities. The spinal fluid pressure and composition were normal, as were roentgenograms of the skull. Routine studies of the blood and urine, including serologic tests, showed no abnormalities.

*Treatment.*—Papaverine hydrochloride, 0.1 Gm., was given three times a day and nicotinic acid, 50 mg. four times a day, for the first three days. The delirium and flaccid hemiplegia persisted. On the fifth day of the illness histamine was substituted for the papaverine and was given once daily for seven days. There was a definite improvement on the fourth day of histamine therapy, the patient beginning to move his left leg, the arm and the fingers. His mental status improved also, with lucid periods most of the day, but still with nocturnal delirium and occasional delusions during the day as well. One month later he was walking behind a wheel chair and he had recovered sufficient function in the fingers to permit handling of utensils and to give a fair grip. He still occasionally was

transiently delusional. He had received nicotinic acid, 50 mg. four times a day, throughout his stay in the hospital. His improvement was still in progress two and one-half months later.

CASE 5.—*Intermittent vascular insufficiency of the left middle cerebral artery with eventual thrombosis.*

*Symptoms.*—A 48 year old man in May 1946 had had an episode of weakness of the right side of the body and inability to talk lasting one day. In June 1948 his speech began to be inexact, with grammatical errors and misuse of words. In August 1948 while working he became dizzy and fell to the floor. Thereafter he could not talk or understand speech.

*Observations.*—On entry he showed a complete motor and sensory aphasia with bilateral positive Babinski signs but no apparent weakness. Except for a blood pressure of 90 systolic and 70 diastolic, the physical examination was otherwise noncontributory. The spinal fluid pressure and chemistry were normal except for a total protein of 65 mg. per hundred cubic centimeters. Roentgenograms of the skull and routine studies of the blood and urine, including serologic tests, showed no abnormalities. Two weeks later hemiplegia developed on the right, and the patient was seen by the neurologic department. He then was unable to walk because of severe weakness of the right leg. He had a complete flaccid paralysis of the arm. He responded to sensory stimuli less on the right and had a right homonymous hemianopsia. There were bilateral pathologic pyramidal reflexes in the lower limbs. He still had a complete motor and sensory aphasia.

*Treatment.*—Infusion of histamine and administration of nicotinic acid, 50 mg. four times a day, were instituted after the development of the hemiplegia. The histamine was administered once a day for nine days, but there was no objective change in the patient's condition other than some increased alertness. Two months later he began to show a voluble paraphasia and the strength improved in his leg. In another month he was walking alone. Four months after the hemiplegia his gait was almost normal. The function had by then also returned to the right hand enough that he could use the fingers to hold utensils and give a weak grip. The sensory deficit was no longer present, and the hemianopsia likewise had cleared. His motor speech was sometimes quite intelligible, but the sensory aphasia was still severe. Recovery is still in progress in the fifth month of his illness. He is receiving speech retraining daily.

## SUMMARY

Early vasodilatation is considered the logical method of salvaging ischemic areas of the brain.

Histamine phosphate given intravenously in a speed of 0.02 mg. per minute produces a consistent dilatation of the arterioles, capillaries and venules of the brain.

This is most conveniently accomplished by administering 2.75 mg. of histamine diphosphate dissolved in 500 cc. of isotonic fluid and given by intravenous drip over a period of two hours.

No change in the arterial or venous blood pressure occurs in man with this speed of intravenous infusion of histamine.

Histamine infusions were given once to three times daily and nicotinic acid administered orally to patients with acute ischemia of the brain.

Twenty-five patients have been followed sufficiently long to evaluate the results of such therapy. One death occurred from an intercurrent uremia. Twenty patients had definite improvement in all affected fields; 3 had improvement in some fields; and 2 had no apparent change during histamine therapy.

Compared to the usual mortality and improvement rates without vasodilatation therapy, these results indicate that histamine therapy was of benefit to these patients.

Intravenous infusion of histamine as described is a safe, readily available, and easily administered method of vasodilatation in cases of acute ischemia of the brain.

Five cases are reported.

The staff of the Birmingham Veterans Administration Hospital, particularly the medical and the neurologic residents, assisted in the study of these cases.

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# STUDIES IN DISORDERS OF MUSCLE

## III. "Pseudohypertrophy" of Muscle in Progressive Muscular Dystrophy and Other Neuromuscular Diseases

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ENLARGEMENT of muscles in progressive muscular dystrophy was noted in the earliest descriptions of the disease.[1] In fact, it has been such a striking finding in many of the cases that a classification has been based on this sign ("pseudohypertrophic" and "atrophic" types).

The enlarged muscles feel doughy on palpation and are weaker than normal. The term "pseudohypertrophy" distinguishes this form of enlargement from real hypertrophy. The latter occurs after intensive use of muscles, as, for example, in weight lifters, and in certain diseases characterized by spasticity of muscles. Grossly, the "pseudohypertrophic" muscles in the muscular dystrophy of childhood show loss of pigment and a "fish flesh" appearance. Microscopically, one finds atrophic fibers and large fibers which stain abnormally and show loss of striation. Intermixed with the normal and abnormal muscle fibers is a great excess of fat and fibrous tissue.

Clinical descriptions of so-called pseudohypertrophic progressive muscular dystrophy in most textbooks leave the impression that the course of the disease proceeds through a stage of enlargement with normal or supernormal strength and is followed by weakness and subsequent atrophy, most of the muscles following this pattern of events. Study of our patients with the progressive muscular dystrophy of childhood [2] has not confirmed this as the typical course. The source of the current teaching is not readily apparent, for the early accounts of pseudohypertrophy do not describe such a process. Barnes [3] did report a family with an unusual type of muscular dystrophy associated with obesity, and

This study was supported by a grant from the United States Public Health Service.

From the Department of Medicine and the Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah College of Medicine.

1. Gowers, W. R.: Pseudohypertrophic Muscular Paralysis, London, J. & A. Churchhill, 1879.

2. Tyler, F. H., and Wintrobe, M. M.: Studies in Disorders of Muscle: I. The Problem of Progressive Muscular Dystrophy, Ann. Int. Med. **32**:72, 1950.

3. Barnes, S.: A Myopathic Family with Hypertrophic, Pseudohypertrophic, Atrophic and Terminal (Distal in Upper Extremities) Stages, Brain **55**:1, 1932.

he concluded, by inference from the fact that the younger members had muscular enlargement and the older ones atrophy, that such a process did occur. However, it should be emphasized that the onset of the disorder in his cases was in adult life, that the condition does not fit any common type of muscular dystrophy and that Barnes himself recognized these deviations from other dystrophies and commented on them in his original report.

In a study of a large group of patients with a variety of neuromuscular disorders, my colleagues and I have made a number of new observations concerning the clinical occurrence and natural history of pseudohypertrophy in muscle. It is the purpose of this paper to report these findings and to discuss their significance.

In a proposed classification of muscular dystrophy presented elsewhere,[2] progressive muscular dystrophy is divided into two types, the childhood and the facioscapulohumeral.

## MATERIAL

The material from which the data for the present report have been drawn is derived from detailed clinical studies on 22 cases of the childhood type of progressive muscular dystrophy, together with 3 cases closely related but deviating from the others in some major characteristic, as well as more than 100 cases of the facioscapulohumeral type and a large number of cases of miscellaneous types of neuromuscular disease in which examination was made concurrently.

A detailed history of a pertinent case is appended. The patient had the childhood type of muscular dystrophy with enlargment of the calf muscles, complicated by an attack of acute anterior poliomyelitis.

## OBSERVATIONS

The 22 patients with the childhood type of dystrophy were males, and in all signs of their disease appeared before the age of 10 years. In the same group will be considered the clinical manifestations in 2 girls and in 1 older man whose disease resembled progressive muscular dystrophy of the childhood type in all respects except for the sex of the patients and the age of onset, respectively (table 2).

At birth and during the early months of life all these subjects had seemed normal. Definite symptoms appeared in 1 patient as early as 18 months of age. In 16 of the 25 patients one or more pairs of muscles were symmetrically enlarged. With respect to the pattern and the mode of progression of muscular loss the entire group was consistent. The pseudohypertrophy was in most cases confined to the calf muscles. A few patients demonstrated a similar abnormality of the deltoid and triceps brachii, and in rare instances of other muscles. In all the enlarged muscles strength was somewhat reduced, although this was remarkably slight as compared with the weakness of the atrophic

muscles in the same body region. Even in patients who were completely bedridden because of weakness and atrophy, the strongest remaining muscles were usually those which originally had manifested the enlargement. In addition, none of the patients gave a clear history of enlargement of muscles which were atrophic at the time of examination, although most of them were very much aware of the abnormal size of the enlarged muscles. In most of the carefully observed patients who had

TABLE 1.—*Pseudohypertrophy in a Group of Patients with Progressive Muscular Dystrophy of Childhood*

| Case No. | Sex | Age, Yr. | Muscular Enlargement | Severity of Disability |
|---|---|---|---|---|
| 1 | M | 7 | + | ++ |
| 2 | M | 7 | + | + |
| 3 | M | 7 | + | + |
| 4 | M | 8 | + | ++ |
| 5 | M | 10 | — | ++ |
| 6 | M | 10 | + | ++ |
| 7 | M | 10 | + | ++ |
| 8 | M | 11 | — | +++ |
| 9 | M | 12 | + | ++ |
| 10 | M | 12 | + | +++ |
| 11 | M | 13 | — | ++ |
| 12 | M | 13 | + | +++ |
| 13 | M | 13 | + | + |
| 14 | M | 13 | + | +++ |
| 15 | M | 14 | + | ++++ |
| 16 | M | 15 | — | ++++ |
| 17 | M | 15 | + | ++++ |
| 18 | M | 17 | + | +++ |
| 19 | M | 19 | + | ++++ |
| 20 | M | 20 | — | ++++ |
| 21 | M | 20 | — | ++ |
| 22 | M | 26 | — | +++ |
| 23 | F | 28 | — | ++ |
| 24 | F | 29 | — | +++ |
| 25 | M | 41 | + | +++ |

pseudohypertrophy, enlargement of the calves had been the first abnormality noted by their parents.

The pattern of muscular loss, age of onset and rate of progress were similar in the patients whether or not they had pseudohypertrophy. Table 1 shows the lack of correlation of severity and muscular enlargement. On the other hand, the correlation of severity and age in cases 1 to 22, inclusive, is evident.

In the case described in the appended report (case 1, table 1) symmetric enlargement of the calves had been present initially. After an episode of poliomyelitis the patient had nearly complete loss of muscle substance in one leg. The atrophy included those muscles which had shown pathologic enlargement before the poliomyelitis (fig. 1).

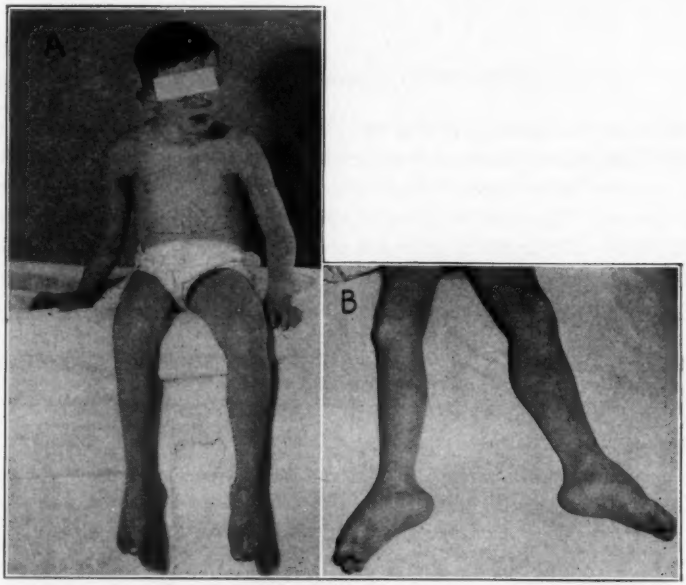


Fig. 1 (case 1, subject of case report).—The striking difference in the degree of atrophy of the right and the left leg is evident. Note particularly the calf muscles and the foot drop. The anterior position of the shoulders and the flat anterior portion of the chest are characteristic of progressive muscular dystrophy. Careful inspection shows the sloping shoulders, which result not from enlargement of the trapezius, but from complete atrophy of its lower fibers with some preservation of its upper fibers and therefore an abnormally high position of the scapulas. The axillary folds slope toward the claviculomanubrial junction instead of toward the xiphoid, as the result of differential atrophy of the sternal and clavicular heads of the pectoralis major. The preservation of the muscles of the forearms in contrast to those of the upper arms, is apparent, but is not marked in degree.

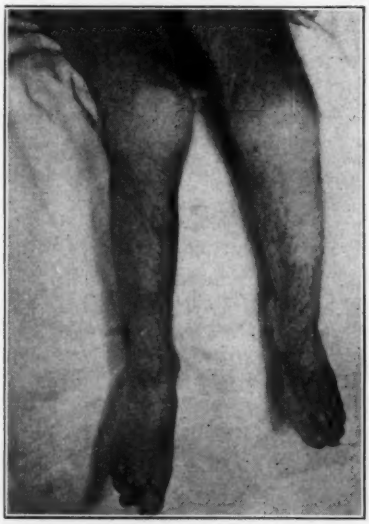

Fig. 2 (case 20, table 1).—Progressive muscular dystrophy of childhood type in a 20 year old youth. The pattern of muscular loss is similar to that in case 1 but is severer. No muscular enlargement is present, and none had been present at any time during this patient's life.

COMMENT

Although there are many and very old descriptions of the clinical findings of "pseudohypertrophy," attempts to explain its pathogenesis have been entirely unsuccessful. Indeed, there is almost no information to be found on the subject. The available histologic description sheds no light on the mechanism of the development of pseudohypertrophy.

The development of atrophy in a previously pseudohypertrophic muscle after damage to the anterior horn cells is surprising in view of the well known fact that the enlargement consists mainly of nonmuscular tissue (fat and fibrous tissue). It would seem that the nonmuscular tissue is in some fashion dependent on the intact lower motor neuron unit for its preservation. Speculation about the significance of this fact does not lead to a sound theory of the pathogenesis of pseudo-

Fig. 3 (case 18, table 1).—Persistence of enlargement of the calf muscles at an advanced stage of progressive muscular dystrophy of childhood. This patient, aged 17, had severe atrophy and weakness of the pelvic, pectoral and axial muscles. He had been unable to walk since 11 years of age. The calf muscles were the strongest of the muscles of the pelvis and the lower extremity.

hypertrophy. The observation does seem to confirm the clinical impression that the fat and fibrous tissue are intimately related to the fundamental disorder of the involved muscles.

As already indicated elsewhere,[2] nearly all cases of progressive muscular dystrophy can be separated into one of two homogeneous groups, which I have called the childhood and the facioscapulohumeral type. The chief differences are outlined in table 2.

In the group with the childhood type the majority of the patients showed pseudohypertrophy of one or more pairs of muscles. In such cases the clinical picture is otherwise identical with that in cases of the childhood type in which no pseudohypertrophy was present. There-

TABLE 2.—*Comparison of Childhood and Facioscapulohumeral Types of Progressive Muscular Dystrophy*

| Type | Childhood | Facioscapulohumeral |
|---|---|---|
| Age of onset | Infancy | Adolescence |
| Type of inheritance | Sex-linked recessive | Dominant |
| Muscles first involved | Pelvic | Pectoral |
| Facial muscles severely affected | No | Usually |
| Pseudohypertrophy | Often present | Rare |

fore the additional division of this type into pseudohypertrophic and atrophic groups does not serve any useful purpose.

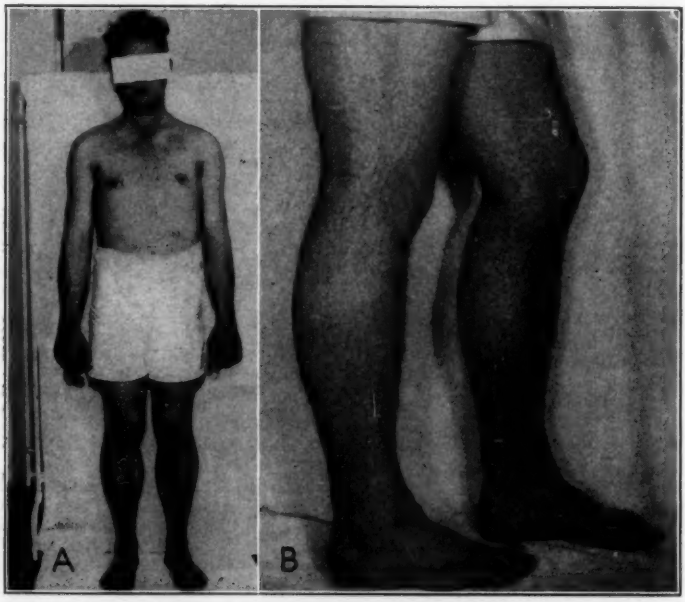


Fig. 4.—Muscular enlargement in a case of familial periodic paralysis. On examination, the calf muscles appeared firm and fibrous, like the pseudohypertrophic muscles of the progressive muscular dystrophy of childhood.

The occurrence of muscular enlargement without increased strength in muscular disorders other than muscular dystrophy of the childhood type is uncommon. We have seen clinically indistinguishable changes in the calf muscles of patients with two other diseases. Of somewhat more than 100 patients with the facioscapulohumeral type of muscular dystrophy which have been seen during the same period as the patients with the childhood type, enlargement of the calves not unlike that seen in the latter group has been observed in 3. In addition, we have under observation a family of which certain members have episodes of weakness

and flaccid paralysis, like those seen in familial periodic paralysis. In these patients enlargement of the calf muscles associated with relative weakness (pseudohypertrophy) has been found.

In the neurologic literature other reports of the occurrence of pseudohypertrophy in familial neuromuscular disorders are to be found, e. g., in Barnes's [8] report. It appears, therefore, that pseudohypertrophy is a useful, but not critically differential, diagnostic point in the recognition of cases of progressive muscular dystrophy of childhood.

## SUMMARY

The occurrence and persistence of muscular enlargement (pseudohypertrophy) in a large group of cases of neuromuscular diseases are discussed. Pseudohypertrophy occurs in many, but not all, cases of the childhood type of muscular dystrophy. It also is seen in an occasional case of facioscapulohumeral dystrophy, in certain cases of familial periodic paralysis and with other neuromuscular disorders. The enlargement may persist in spite of extreme progression of the primary muscular disorder which characterizes progressive muscular dystrophy.

The case is presented of a boy who had the muscular dystrophy of childhood with pseudohypertrophy of the muscles of the calves and who, after an episode of poliomyelitis, had unilateral atrophy of the calf muscles.

It is concluded that pseudohypertrophy is dependent on an intact lower motor neuron unit.

## REPORT OF A CASE

D. A., a 7 year old boy, had manifested enlargement of the calf muscles, obvious to his parents, at the age of 3 years. This condition was bilaterally symmetric and progressive. During the next three years there developed, rather insidiously, muscular weakness of the trunk and hips and foot drop. Lordosis and a waddling, grotesque gait of the type usually seen in early dystrophy gradually appeared. At the age of 6 years he had an acute illness with headache and fever, followed by pain and rapidly progressive weakness in the right lower extremity. He experienced difficulty in initiating urination on one or two occasions, and slight nuchal rigidity then developed. Lumbar puncture showed a maximum of 10 lymphocytes per cubic millimeter of cerebrospinal fluid, and the total protein was as high as 63 mg. per hundred milliliters. There then developed extensive paralysis, most marked in the right leg. Since that time this leg had become very atrophic, in contrast to the left, in which the enlargement of the calf muscles had persisted. The patient had required a brace and crutches for walking.

*Personal History.*—The patient's birth and early development were normal. He had had measles, chickenpox and mumps, without complications. Except for occasional infections of the respiratory tract, he had been well and had had no operations or serious injuries.

*Family History.*—A 10 year old brother (case 7, table 1) had progressive muscular dystrophy of childhood, which was severer than the patient's disease.

There was symmetric enlargement of the calves. He also had bilateral colobomas of the iris and retina. The maternal grandfather was said to have had clubfeet. A maternal aunt and the maternal grandmother had diabetes mellitus. There were no other known members of the family with neuromuscular or hereditary disease.

*Physical Examination.*—The boy was thin but rather tall for his age. The temperature and respiration were normal; the pulse rate was 110. The blood pressure was 92 systolic and 60 diastolic. There was no definite weakness, atrophy or asymmetry of the face, but the expression was rather "flat," an appearance which characterized other, nondystrophic members of the family. The lower lip protruded a little. The pupils, extraocular muscles and fundi were normal. The proximal muscles of the shoulder girdle showed definite weakness and atrophy, which were most pronounced in the lower part of the trapezius, the rhomboideus, the latissimius dorsi, the serratus anterior and the sternal head of the pectoralis major, bilaterally. The deltoid, biceps and triceps brachii on both sides were of moderate volume but were considerably reduced in strength. The muscles of the forearm and hand were essentially normal, although the strength was not as great as one might expect in a child of 7 years. The spinal musculature was reduced in volume and was weak but was adequate to raise the trunk against gravity. The boy stood with a prominent lumbar lordosis. All the muscles above the pelvic girdle were symmetric in their respective degrees of involvement. On the left side there were weakness and atrophy of all the muscles of the hip and thigh, but these signs were severest in the quadriceps and the abductors of the thigh. Considerable strength remained in all groups. The lower left leg showed marked weakness and atrophy of the peroneal and tibial muscle groups, resulting in a typical foot drop. The calf muscles were larger than one might expect in a boy of 7; their strength was fairly good, and they were of firmer consistency than usual. As compared with the other muscles of the left leg, the calf group and the intrinsic muscles of the foot were the stronger. In striking contrast, the muscles of the right thigh and leg, including the calf muscles, were greatly reduced in strength and mass throughout (fig. 1). Almost no detectable muscle tissue was present in the lower leg or the foot on this side. The pelvic musculature on the right side was relatively good and was comparable to that on the left. The right leg was about 3 cm. shorter than the left and showed definite atrophy. The patient's gait and lordosis were only a little modified from those of his dystrophic brother.

The neurologic examination gave normal results except for decreased tendon reflexes, consistent with the loss of muscle substance.

The remainder of the physical examination showed nothing remarkable.

*Laboratory Data.*—Examination of the blood showed a volume of packed red cells of 42 ml. per hundred milliliters. The white blood cell count, smear and differential count were normal. The urine and stool were normal. The serologic test for syphilis gave a negative reaction. The fasting blood sugar was 87 mg. per hundred milliliters of blood. The electrocardiogram showed sinus tachycardia and curves consistent with a normal but vertically placed heart. The urinary creatinine excretion on a creatine-free diet was 188 mg. per twenty-four hours, with a total creatine-creatinine content of 475 mg. per twenty-four hours (expressed as creatinine). These values indicate that there was a greatly reduced excretion of creatinine and greatly increased excretion of creatine in the urine as compared with values for normal boys of the same age.

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# CHANGES IN BEHAVIOR FOLLOWING FRONTAL LOBECTOMY IN DOGS AND CATS

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INTEREST in the function of the frontal lobes has greatly increased since Moniz'[1] proposal to disconnect them surgically from the rest of the brain. In studies on the role of the cerebral cortex in the regulation of the activity of the autonomic nervous system,[2] this problem attracted our attention. Not only was the presence of specific "autonomic centers" in the frontal lobes considered possible, but it was realized that the changes in behavior in animals after frontal lobectomy might affect the activity of autonomically controlled organs. It was necessary, therefore, to study the objective evidence for such changes in dogs and cats after ablation of various portions of the frontal lobes, with particular regard to the manifestations of autonomic imbalance.

## LITERATURE

In 1909 one of us (B. P. B.)[3] studied the effect of the ablation of frontal lobes in 4 dogs, using the method of conditioned reflexes. All the brain anterior to the cruciate and the inferior end of the presylvian sulcus, including the olfactory bulbs and tracts, was removed. After operation there was no change in the conditioned auditory or visual reflexes, and new ones could be formed easily. However, conditioned reflexes to tactile stimuli (brushing or very gentle pricking of the skin

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From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

1. Moniz, E.: Tentatives operatoires dans le traitement de certaines psychoses, Paris, Masson et Cie, 1936.

2. Babkin, B. P., and Speakman, T. J.: Cortical Inhibition of Gastric Motility, J. Neurophysiol., to be published.

3. Babkin, B. P.: Concerning the Function of the Frontal Lobes in the Dog, Tr. Imperial Mil.-M. Acad., St. Petersburg, 1909, pp. 16 and 109.

of the body) were greatly weakened or could not be formed. Of particular interest was the "reaction of resistance," which consisted in struggling of the animal without any sign of rage. This response appeared when the animal was restrained in the usual manner in the testing stand, but was not apparent when it was allowed freedom of movement. Magoun and Ranson [4] reported the same phenomenon in lobectomized cats. The "reaction of resistance" (or "reaction to restraint," as it is better called) differed greatly from rage and "sham rage."

Thus, a more extensive removal of the anterior half of the cerebral hemispheres (anterior to the sigmoid gyrus and the sylvian fissure), including the olfactory tracts and bulbs,[5] changed the "reaction of resistance" to one of rage, which could be provoked by merely touching the animal. All conditioned reflexes formed before the operation disappeared and could not be restored. The only one that could be formed after the operation was the "water" reflex. This rage resembled that which Goltz [6] described in his totally (?) decorticate dog.

Many investigators (for a survey of the literature, see Bard and Mountcastle [7]) explained the sham rage in decorticate animals as a result of the loss of cortical inhibition of the hypothalamic centers. However, the removal of different parts of the cerebral cortex may produce opposite effects. Recently cats were rendered "placid" by ablation of all the neocortex,[7] and this state of placidity was converted to one of ferocity by removal of the cingulate gyrus and anterior limbic area or of certain rhinencephalic structures (amygdaloid nucleus, pyriform lobe and hippocampus).

The center for "hyperactivity" (spontaneous movement not evoked by any sort of restraint) has been localized in the frontal lobes by Jacobsen.[8] Ruch and Shenkin [9] stated the belief that hyperactivity most consistently follows removal of area 13 on the orbital surface (in

4. Magoun, H. W., and Ranson, T. W.: Behavior of Cats Following Bilateral Ablation of Rostral Portions of the Cerebral Hemispheres, J. Neurophysiol. **1**:39, 1938.

5. Pavlov, I. P.: Conditioned Reflexes, translated by G. V. Anrep, London, Oxford University Press, 1927, pp. 353 and 364.

6. Goltz, F.: Der Hund ohne Grosshirn: Siebente Abhandlung über die Verrichtungen des Grosshirns, Arch. f. d. ges. Physiol. **51**:570, 1892.

7. Bard, P., and Mountcastle, V. B.: Some Forebrain Mechanisms Involved in Expression of Rage, with Special Reference to Suppression of Angry Behavior, A. Research Nerv. & Ment. Dis., Proc. (1947) **27**:362, 1948.

8. Jacobsen, C. F.: The Frontal Lobes: A Study of Cerebral Function in Learning, J. Comp. Neurol. **52**:271, 1931.

9. Ruch, T. C., and Shenkin, H. A.: The Relation of Area 13 on the Orbital Surface of the Frontal Lobes to Hyperactivity and Hyperphagia in Monkeys, J. Neurophysiol. **6**:349, 1943.

monkeys) and that lesions of areas 8 to 12 produce a milder form with a longer latent period. Fulton and his co-workers[10] have confirmed this observation.

While it seems that the removal of certain regions of the cerebral cortex may lead to the "release" of the diencephalon from cortical control, it must be kept in mind that many such preparations have suffered the loss of part of the basal ganglia and/or the thalamus.[11] Bard and Rioch[12] showed that when the subcortical structures were involved in the operation in animals there appeared excessive fear and rage, sexual indifference and no visible expression of pleasure. This perhaps explains the reported appearance of sham rage in cats after removal of the frontal lobes, since it would appear from the illustrations that there must have been some damage to the basal ganglia.[13] However, a more precise definition of the role of the frontal lobes in the autonomic components of behavior and emotion seemed desirable.

## METHODS

Under aseptic conditions, 5 dogs and 3 cats underwent varying degrees of removal of the anterior pole of the brain by subpial suction.

*Dogs.*—Cerebral ablations of four types were performed on 5 dogs, the procedures being arbitrarily designated as follows (fig. 1):

1. Frontal. Removal of all the cerebral tissue anterior to a coronal plane through the medial end of the cruciate sulcus, including the olfactory tracts (dog 1).

2. Prefrontal. Ablation of all the cerebral tissue anterior to a coronal plane through the superomedial end of the presylvian sulcus, the olfactory bulbs and tracts being removed (dogs 2 and 5) or left intact (dog 3).

3. Precruciate. Removal only of the cortex of the precruciate gyrus and the anterior end of the coronal gyrus (dog 3). This procedure served as a control.

4. Insular-orbital. Removal of the cortex of the anterior and posterior sylvian gyri, the anterior end of the ectosylvian gyrus and a small portion of the anterior coronal gyrus and the posterior angle of the prefrontal lobe (dog 4). (This region of the cerebral cortex in the dog may be considered analogous to the anterior part of the island of Reil, and probably part of the orbital surface, in man.[14])

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10. Fulton, J. F.; Livingstone, R. B., and Davis, S. D.: Ablation of Area 13 in Primates, Federation Proc. **6**:108, 1947.

11. Bard, P.: On Emotional Expression After Decortication with Some Remarks on Certain Theoretical Views, Physiol. Rev. **41**:309, 1934.

12. Bard, P., and Rioch, D. McK.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:73, 1937.

13. Kennard, M. A.: Focal Autonomic Representation in the Cerebral Cortex and Sham Rage, J. Neuropath. & Exper. Neurol. **4**:295, 1945.

14. Ariëns Kappers, C. U.; Huber, C. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System, New York, The Macmillan Company, 1936, vol. 2, p. 1542.

The 5 male dogs of this series were observed for three to four weeks before operation to allow them to become accustomed to the routine of the animal house and to ascertain their normal habits and responses to various stimuli under these conditions. Three (dogs 2, 3 and 4) were judged to be within the average limits of "normal." Dog 1 was slightly more timid than usual, and dog 5 was an extremely vicious, almost wild, animal. All except dog 5 possessed metal gastric fistulas.

*Cats.*—A series of operations were performed on 3 adult cats in order to compare the changes with those observed in dogs (fig. 2).

1. Prefrontal. Removal of the gyrus proreus, leaving the olfactory tracts intact, a procedure corresponding to removal of the "prefrontal lobe" in the dog (cat 1).

2. Frontal. Removal of all the cerebral tissue anterior to a coronal plane through the medial end of the cruciate sulcus and including the olfactory tracts (cat 2).

3. Ablation of the cerebral tissue anterior to a coronal plane through the ansate sulcus. During the gradual sucking away of tissue, the anterior end of the corpus striatum was identified and spared. The removal extended just into the anterior horns of the lateral ventricles (cat 3).

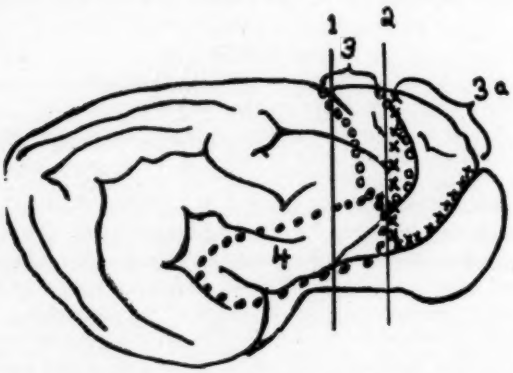


Fig. 1.—Sketch of lateral aspect of the dog brain.

*1*, frontal cerebral ablation (dog 1); *2*, prefrontal cerebral ablation, including olfactory tracts (dogs 2 and 5); *3* (circles), precruciate cortical removal, as a control (dog 3); *3a* (crosses), prefrontal cerebral ablation, with olfactory tracts and bulbs left intact (dog 3); *4* (dots), insular-orbital cortical removal (dog 4).

## RESULTS

*Dogs.*—In the accompanying table are summarized the results of various operations on the behavior and autonomic manifestations of the experimental animals. To make certain that the intracranial procedures and surgical damage per se to any part of the cerebral cortex did not produce the reactions to be described, the precruciate cortex was removed in dog 3 before ablation of the frontal lobes. No behavior changes were observed after this control operation.

Reaction to Restraint: It was demonstrated in dogs 1, 2 and 3 that bilateral removal of larger or smaller portions of the frontal pole of the brain so altered the character of the animals that a strong emotional reaction could be induced by restraint. Speaking in objective terms, the "reaction to restraint" was an exaggerated normal response to restriction of movement without the manifestations of rage.

The mildest "reaction to restraint" was observed when the prefrontal lobes were removed and the olfactory bulbs and tracts were preserved (dog 3). This reaction was greatly enhanced by simultaneous removal of the olfactory bulbs and tracts (dog 2). It achieved its maximal expression when the whole anterior part of the brain was

*Results of Various Types of Frontal Lobectomy on Behavior and Autonomic Manifestations in Dogs*

| Ablation | Dog No. | Reaction to Restraint | | Reaction to "Startle," Days | Autonomic Manifestation During Restraint | Hyperactivity | |
|---|---|---|---|---|---|---|---|
| | | Severity | Duration, Days | | | Severity | Duration, Days |
| Frontal ..... | 1 | +++ | 60 | 78 | Snarling respiration; arching back; extrusion of claws; dilation of pupil; slight piloerection; hypersalivation; dribbling of urine | + | 14 |
| Prefrontal, including olfactory tracts | 2 | ++ | 19 | 33 | Snarling respiration; arching back; extrusion of claws; lashing of tail | — | — |
| Prefrontal, leaving olfactory tracts | 3 | + | 10 | 23 | Rapid respiration | — | — |
| Insular-orbital ..... | 4 | — | — | — | — | ++++ | 28 |

ablated in front of the cruciate sulcus (dog 1), but it did not contain any element of rage. It could be elicited by any type of restraint.

Before operation the animal was accustomed to stand for two to three hours quietly in a stand supported by two wide, soft bands of cloth; after operation, placing it in the stand induced the reaction to be described. The response could be evoked equally well by merely holding the animal as it walked about the room.

In an extreme case (dog 1) the "reaction to restraint" consisted of violent struggling, clawing and scratching the floor of the stand (coordinated to "back away" from the restraining influence); yelping, snarling and even a defensive type of snapping occurred when a hand or other object was rapidly moved toward the dog. Associated with these somatic outbursts were pupillary dilation, extrusion of the claws, perhaps slight piloerection, hypersalivation and occasionally dribbling of urine. In this particular dog the described reaction was maintained

up to two hours and could be diminished only slightly by petting. In spite of the violence of the reaction and autonomic manifestations, the response did not have the traits of rage. When the animal was released and placed on the floor, the reaction immediately ceased, and it never occurred with any stimulus other than restraint. It gradually diminished with time and had almost disappeared nine weeks after the operation. Yet in 2 cats which were subjected to removal of rhinencephalic structures [7] the reaction of rage acquired a permanent character and persisted eight and a half and eight months, respectively, until the end of the observational period.

The same manifestations were observed, but in a milder form, in dogs 2 and 3 (table). In dog 2, after "prefrontal" ablation including the olfactory tracts, the reaction to restraint was intermittent, with quiescent intervals of three to five minutes. The autonomic manifestations were not so severe. During the fourth postoperative week a conditioned gastric-secretory reflex was quickly formed (on the sixth day) through the combination of sham feeding with meat and ringing of a bell. In dog 3 in which the precruciate cortex and the prefrontal lobes had been removed but the olfactory bulbs and tracts had been preserved, the reaction to restraint was definitely present but was expressed weakly. Four weeks after the operation the animal no longer reacted to any form of restraint.

In the later postoperative periods the "reaction to restraint" became intermittent, and all the dogs would stand quietly for periods in the testing stand. At such times the reaction could be induced by a sudden "startling," threatening action.

Dog 5 was an extremely vicious, almost wild, animal which would allow no one to handle it. It was subjected to a prefrontal lobectomy with removal of the olfactory tracts (similar to dog 2) in order that the effects of the procedure on this type of behavior might be observed. After operation there was no diminution in its antagonism; it was impossible to determine whether there had been an increase. The dog was observed in this state for two months and then killed.

Hyperactivity: Three and one-half weeks after the operation, especially during the fourth and fifth weeks, dog 1 also began to show another type of abnormal behavior similar to what has been described as hyperactivity. When left free, the animal would walk rapidly, continuously and aimlessly from one end of the room to the other over almost identical routes, without pause or variation at either end. At no time during our observation of this phenomenon did the dog show the slightest emotional change if its movements were undisturbed.

More interesting were the results of bilateral removal of the insular-orbital cortex in two stages in dog. 4. After the first operation the dog showed moderate hyperactivity with some circling movement toward the side of removal. After the second operation the animal maintained per-

sistent aimless hyperactivity to the point of exhaustion. It would walk around and around in its cage for several hours before collapsing. If semisuspended in the testing stand, the dog rested its body on supports (loops of soft cloth) and continued rapid coordinated walking movements without cessation. There were never any manifestations of rage, and there was no sign of "reaction to restraint" or autonomic imbalance unless its legs were immobilized, when it struggled and vocalized loudly.

After the first postoperative week the aimless motor activity began to stop for short periods, and these intervals became more and more frequent with time. The hyperactivity could be arrested for a short period by petting, or, if the animal was quiet, initiated by entry of the observer into the animal room.

The dog was fed through its gastric fistula until the seventh day, when it began to eat spontaneously, taking a mouthful of food during

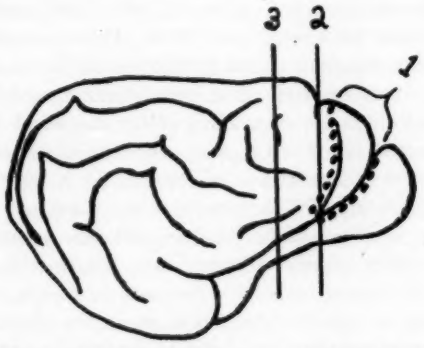


Fig. 2.—Sketch of lateral aspect of the cat brain.
*1*, prefrontal ablation of gyrus proreus (cat 1); *2*, frontal ablation (cat 2); *3*, ablation anterior to coronal plane through ansate sulcus (cat 3).

each circuit around the cage but never fully stopping. As the hyperactivity gradually subsided, it began to stop to eat for longer intervals. By the fifth week this hyperactivity had disappeared and could not be induced by any stimulus, the behavior returning to the preoperative normal.

*Cats.*—Quite different results were observed in cats after ablation of various portions of the frontal pole of the brain (fig. 2).

In cat 1, with a prefrontal removal and the olfactory tracts left intact, no behavior changes were observed after operation.

In cat 2, all the cerebral tissue, including the olfactory tracts, was removed anterior to a coronal plane through the medial end or the cruciate sulcus. After operation this animal did well and showed no excessive rage in response to painful stimulation, mild or severe. On the contrary, there was a greater show of desire for affection, and pet-

ting was avidly sought. If confined to its cage when the observer was in the room, this cat continuously cried until attention was turned in its direction. Then it would purr loudly and rub its arched back against the cage door. When released, it followed the observer and demanded petting. This condition persisted until the animal was killed, six weeks later.

Ablation of the frontal part of the brain anterior to a coronal plane through the ansate sulcus was performed on cat 3. As was pointed out in the section on "Methods," both the anterior end of the corpus striatum and the thalamus were spared during the operation on this animal. Walking and chewing movements of course were spastic in the early postoperative period. There resulted apparent analgesia so that the tail could be stepped on with perhaps 50 pounds (22.7 Kg.) of pressure or bent to the breaking point, the whiskers pulled, the incision manipulated or pins driven through the skin into the muscles, without response. This state persisted up to the end of the observation period of four weeks, when the animal was killed. For two weeks the lack of response to painful stimulation was coupled with the loss of reaction to obstacles, food, observer, etc. The only stimulus which would elicit somatic movements was the suspending of the animal by the nape of its neck. This caused some struggling, superimposed on the normal postural movements and extrusion of the claws. Neither with this nor with painful stimulation did the animal ever show any sign of rage. Occasionally we observed slight pupillary dilation as an isolated phenomenon in response to painful stimulation, but this was neither constant nor marked. Analogous lack of response to nociceptive stimulation has been reported in cats with the whole neocortex ablated.[7]

From the fourteenth day, an "arrest" reaction could be evoked in cat 3 by strong stimuli. Painful stimulation applied to the tail of the animal during walking movements caused abrupt cessation of this activity, retraction of the body backward onto the flexed hindlimbs and gradual extension and rotation of the head, neck and body, so that the animal was eventually looking directly at the source of stimulation. No attempt was ever made to bite the offending instrument or to escape from it, and no rage reaction could be observed. On release from the nociceptive stimulus, walking movements immediately returned.

Studies on this short series of cats showed that removal of larger or smaller portions of the frontal pole of the brain produced certain alterations in the animals' behavior, but that so long as the basal ganglia were not disturbed the autonomic components of sham rage were not manifest.

## COMMENT

The observations reported in the preceding section show that there is a definite species difference between dogs and cats in the reaction

to various stimuli and in the general behavior after removal of similar cortical areas.

The most characteristic phenomenon observed in dogs after the prefrontal and frontal ablations was the "reaction to restraint." For a short period hyperactivity was also observed, but rage was never seen. The "reaction to restraint" was produced in increasing severity by progressively larger removals of the frontal lobes and was augmented by simultaneous ablation of the olfactory tracts. It was accentuated, and in its minimal stages it was produced only by an unexpected and "startling" restraint or a threatening action. The reaction was associated with some autonomic manifestations in a degree proportionate to the severity and duration of the limitation imposed on the movements of the animal.

The impulse to liberate oneself from a restraining force is an important component of the instinct of self preservation in the whole animal kingdom. This reflex, essentially unconditioned, but probably with a superimposed conditioned part, is kept in check presumably by influences deriving from the frontal lobes. After the removal of these structures, on the slightest provocation, this reflex is displayed in all its strength. Lobectomy accentuates the normal reaction of most of the dogs placed for the first time in the testing stand. This reaction consists in an attempt of the animal to liberate itself from the restraining supports, coupled with such manifestations as rapid respiration and continuous salivation. It is interesting to note that Pavlov [15] observed this phenomenon in a highly exaggerated form in a dog which had not been operated on and called it a "reflex of freedom." Subsequently, he was able to inhibit the "reflex of freedom" by conditioning the animal to feeding during restraint.

From the "reaction to restraint" another behavioral complex must be distinguished—sham rage. Sufficient evidence has been presented in this study to show that frontal lobectomy does not facilitate the appearance of rage, and that the "reaction to restraint" cannot be looked on as a mild expression of rage, since the patterns of these two reactions are different. Although they have some traits in common, e. g., arching of the back or extrusion of claws, the chief component of rage, i. e., the attempt to bite, was completely absent in lobectomized dogs, or appeared only as a defensive mechanism. The significant differentiating feature, however, was the complete absence of the reaction to restraint in response to any stimulus except restraint. Sham rage, on the other hand, is evoked by a multitude of often mild stimuli. From human experience it is known that the "reaction to restraint" may be coupled not only with rage but also with fear.

15. Pavlov, I. P.: Lectures on Conditioned Reflexes, translated by W. H. Gantt, New York, International Publishers, 1928.

For the development of rage the primitive olfactory system seems to be essential. Bard and Mountcastle [7] advanced a hypothesis that the area of the amygdaloid nucleus acts as a funnel through which inhibitory influences which originate in the transitional cortex of the midline, in the neocortex and in the amygdaloid nucleus itself exert a suppressing action on diencephalic mechanisms, presumably in the ventromedial hypothalamic nuclei. If this hypothesis can be proved, a link between the frontal lobe and the olfactory-hypothalamic unit has to be found for a proper interpretation of the reaction to restraint. Papez [16] stated the belief that such integration could be achieved through the subcallosal fasciculus which connects the frontal, cingular and parietal cortex with the hippocampal formation.

It has been seen that removal of the frontal lobe in cats produces quite a different result than in dogs. It is difficult to express in physiologic terms the type of behavior changes in such cats. One still is forced to use such vague terms as "rage," "placidity" and "reaction to restraint." After a "prefrontal" ablation, the cat, as a psychologist would say, becomes more friendly, and even affectionate. More definite results were obtained in the cat after a "frontal" removal: The animal lost completely the vigorous defense reaction to nociceptive stimuli. In this respect our results are in agreement with those of Barris.[17] The behavior of our cats deprived of the frontal lobes was very much like the "placid" behavior of cats with the whole neocortex removed.[7] But we have not been able to confirm the statement [18] that sham rage results from removal of the frontal cortex in cats. It may be that for the development of this reaction the involvement of either the primitive olfactory system [7] or the basal ganglia [11] is also necessary.

It is also interesting that the "arrest" response which has been described was observed in this laboratory during thalamic stimulation by implanted electrodes. The behavior of these cats may well be compared to the picture in man after prefrontal lobectomy. While he is momentarily aware of pain, there is a more or less complete loss of affective behavior in response thereto.

SUMMARY

There is a species difference between dogs and cats in the reaction to various stimuli and in general behavior after removal of the frontal lobes.

16. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725 (Oct.) 1937.

17. Barris, R. W.: Cataleptic Symptoms Following Bilateral Cortical Lesions in Cats, Am. J. Physiol. **119**:213, 1937.

The most typical phenomenon observed in dogs after prefrontal or frontal ablation was the "reaction to restraint" without any manifestations of rage.

The intensity of the "reaction to restraint" increased with progressively larger removals of the frontal lobes and with simultaneous ablation of the olfactory bulbs and tracts. This reaction was associated with autonomic hyperactivity, the intensity of which increased in proportion to the amount of frontal brain tissue ablated.

Ablation of a region of the cortex in the dog corresponding in part to the island of Reil and the orbital surface in man induced only hyperactivity.

Prefrontal and frontal ablations never produced a rage reaction in cats, but, on the contrary, made them more friendly or indifferent. A more extensive removal of the frontal pole (anterior to the coronal plane through the ansate sulci) abolished the usual reaction to nociceptive stimuli.

Montreal Neurological Institute.

# SODIUM CONCENTRATION OF THERMAL SWEAT IN TREATED AND UNTREATED PATIENTS WITH MENTAL DISEASE

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AND
MARK D. ALTSCHULE, M.D.
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THERE is evidence that treatment of mental disease results in strong stimulation of the adrenal gland; increased secretion of steroid hormones is suggested by studies on the change in lymphocytes and eosinophils in the blood, the uric acid–creatinine ratio and changes in the extracellular fluid volume after shock therapy.[1] In an attempt to gain insight into the activity of the adrenal gland in relation to salt and water metabolism in mental disease and during the course of treatment, it was decided to study the sodium concentration of sweat in patients.

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From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass., and the Department of Medicine, Harvard Medical School.

1. (*a*) Godlowski, Z. Z.: Eosinopenia Caused by Adrenaline Infusion and by Insulin Hypoglycemia, Brit. M. J. **1**:47, 1948. (*b*) Mikkelsen, W. P., and Hutchens, T. T.: Lymphopenia Following Electrically Induced Convulsions in Male Psychotic Patients, Endocrinology **42**:394, 1948. (*c*) Altschule, M. D.; Altschule, L. H., and Tillotson, K. J.: Changes in Leukocytes of the Blood in Man After Electrically Induced Convulsions, Arch. Neurol. & Psychiat. **62**:624 (Nov.) 1949; (*d*) Changes in Urinary Uric Acid–Creatinine Ratio After Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **9**:548, 1949. (*e*) Parsons, E. H.; Gildea, E. F.; Ronzoni, E., and Hulbert, S. Z.: Comparative Lymphocytic and Biochemical Responses of Patients with Schizophrenia and Affective Disorders to Electroshock, Insulin Shock, and Epinephrine, Am. J. Psychiat. **105**:573, 1949. (*f*) Altschule, M. D.; Parkhurst, B. H., and Tillotson, K. J.: Decreases in Blood Eosinophilic Leukocytes After Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **9**:440, 1949. (*g*) Altschule, M. D.; Ascoli, I., and Tillotson, K. J.: Extracellular Fluid and Plasma Volumes in Depressed Patients Given Electric Shock Therapy, Arch. Neurol. & Psychiat. **62**:618 (Nov.) 1949. (*h*) Altschule, M. D., and Tillotson, K. J.: Effect of Electroconvulsive Therapy on Water Metabolism in Psychotic Patients, Am. J. Psychiat. **105**:829, 1949. (*i*) Altschule, M. D.; Cline, J. E., and Tillotson, K. J.: Fall in Plasma Protein Level Associated with Rapid Gain in Weight During Course of Electro-Shock Therapy, Arch. Neurol. & Psychiat. **59**:476 (April) 1948, (*j*) Altschule, M. D.; Grunebaum, H., and Promisel, E.: Significance of Changes in Extracellular Fluid Volume in Insulin Therapy for Mental Disease, J. Applied Physiol., to be published. (*k*) Altschule, M. D., and Tillotson, K. J.: Effects of Electric Convulsive Therapy on Diuretic Response to Water in Psychotic Patients, Arch. Neurol. & Psychiat. **61**:188 (Feb.) 1949.

## MATERIAL AND METHODS

Studies were made on 7 nonpsychotic men, 9 nonpsychotic women, 16 psychotic men and 19 psychotic women. The ages ranged from 20 to 76, and the diagnoses were varied (tables 1 and 2). Some of the patients had been ill for long periods, but none was severely deteriorated (table 2).

The method of sweat collection was as follows: The patient washed and dried his hands and arms to above the elbows and put on a pair of clean obstetric rubber gloves; he then sat, with the head out, in a box heated by electric light bulbs to approximately 110 F. Between 5 and 25 cc. of sweat was collected in the gloves in eight to thirty minutes. The sweat was then analyzed for sodium with a Perkin and Elmer "flame spectrophotometer."

TABLE 1.—*Data on Nonpsychotic Subjects*

| Case Number | Sex | Age, Years | Sweat Sodium, mEq. | Diagnosis |
|---|---|---|---|---|
| 1..... | M | 43 | 30 | Normal |
| | | | 29 | |
| 2..... | M | 23 | 30 | Normal |
| 3..... | M | 29 | 34 | Normal |
| 4..... | M | 29 | 63 | Normal |
| 5..... | F | 23 | 50 | Normal |
| | | | 62 | Normal |
| 6..... | F | 21 | 50 | Normal |
| 7..... | F | 26 | 32 | Normal |
| 8..... | F | 20 | 57 | Normal |
| 9..... | F | 21 | 29 | Normal |
| | | | 30 | |
| | | | 31 | |
| 10..... | F | 20 | 33 | Normal |
| | | | 31 | |
| | | | 41 | |
| 11..... | M | 59 | 59 | Anxiety |
| 12..... | M | 33 | 44 | Alcoholism |
| 13..... | M | 38 | 45 | Alcoholism |
| 14..... | F | 39 | 41 | Psychoneurosis—reactive depression |
| 15..... | F | 41 | 30 | Psychoneurosis—reactive depression |
| 16..... | F | 33 | 41 | Psychoneurosis—reactive depression |

## OBSERVATIONS

The sodium concentration of sweat in 16 nonpsychotic subjects ranged from 29 to 63 milliequivalents (table 1). Values for repeated determinations on subjects with normal sodium concentrations of the sweat were usually within 12 milliequivalents of each other, and the average deviation was ± 2.3 milliequivalents (tables 1 and 2). When greater variations were found, they were due to determinations having been made after exhausting exercise or late in the menstrual period.[2] Greater variations occurred in 2 psychotic patients (cases 17 and 20, table 2) with high sweat sodium concentrations.

Measurements made on 21 psychotic subjects before treatment revealed values ranging from 15 to 128 milliequivalents; 12 of the values

2. Altschule, M. D., and Grunebaum, H.: To be published.

TABLE 2.—*Data on Psychotic Subjects*

| Case Number | Sex | Age, Years | Sweat Sodium mEq. | Diagnosis | Duration of Illness | Comment |
|---|---|---|---|---|---|---|
| 17 | M | 47 | 77 | Schizophrenia, hebephrenic | 31 yr. | |
| | | | 56 | | | |
| 18 | M | 46 | 40 | Manic-depressive psychosis, manic phase | 12 yr. | 20th day of a period of electric shock therapy |
| | | | 34 | | | 23d day of a period of electric shock therapy |
| | | | 44 | | | 25th day of a period of electric shock therapy |
| | | | 40 | | | 31st day of a period of electric shock therapy |
| 19 | M | 32 | 35 | Schizophrenia, hebephrenic | 8 yr. | Seven months after leukotomy |
| 20 | M | 25 | 128 | Schizophrenia, simple | 3 yr. | |
| | | | 92 | | | |
| | | | 77 | | | |
| 21 | M | 19 | 40 | Schizophrenia, catatonic | 6 mo. | After 1 month of insulin therapy |
| | | | 43 | | | After 1 month of insulin therapy |
| | | | 48 | | | After 1 month of insulin therapy |
| | | | 40 | | | Third day of a period of electric shock therapy |
| 22 | M | 28 | 60 | Manic-depressive psychosis, manic phase (discharged) | 1 yr. | |
| | | | 56 | | | Twenty days later; disease in remission |
| 23 | M | 28 | 58 | Manic-depressive psychosis, manic phase (discharged) | 2 yr. | Before therapy |
| | | | 37 | | | Six hours after first electric shock |
| | | | 40 | | | Seventh day of period of electric shock |
| | | | 37 | | | Eighth day of period of electric shock |
| 24 | M | 36 | 93 | Schizophrenia, unclassified | 12 yr. | Before therapy |
| | | | 75 | | | Third day of period of insulin therapy |
| | | | 69 | | | Seventeenth day of period of insulin therapy |
| 25 | M | 25 | 26 | Schizophrenia, paranoid | 2 mo. | Before therapy |
| | | | 18 | | | Third day of period of insulin therapy |
| | | | 22 | | | Thirty-first day of period of insulin therapy |
| 26 | M | 27 | 85 | Schizophrenia, hebephrenic | | Before therapy |
| | | | 51 | | | Tenth day of period of insulin therapy |
| 27 | M | 54 | 51 | Schizophrenia, paranoid | 1 yr. | Before therapy |
| | | | 43 | | | Eleventh day of period of electric shock therapy |
| 28 | M | 51 | 84 | Schizophrenia, paranoid | 3 yr. | |
| | | | 80 | | | |
| 29 | M | 30 | 55 | Schizophrenia, unclassified | 14 yr. | Three years after leukotomy |
| 30 | M | 50 | 100 | Schizophrenia, hebephrenic | 20 yr. | Three months after leukotomy |
| 31 | M | 42 | 50 | Schizophrenia, hebephrenic | 20 yr. | Five months after leukotomy |
| 32 | F | 22 | 46 | Schizophrenia, catatonic | 2 mo. | Sixth day of period of electric shock therapy |

TABLE 2.—*Data on Psychotic Subjects—Continued*

| Case Number | Sex | Age, Years | Sweat Sodium mEq. | Diagnosis | Duration of Illness | Comment |
|---|---|---|---|---|---|---|
| 25 | F | 57 | 67 | Manic-depressive psychosis, depressed | 1 yr. | Four months after leukotomy |
| 34 | F | 59 | 59 | Schizophrenia, paranoid | 16 yr. | Four months after leukotomy |
| 35 | F | 30 | 65 | Schizophrenia, catatonic | 7 yr. | Four years after leukotomy |
| | | | 67 | | | |
| 36 | F | 42 | 21 | Manic-depressive psychosis, depressed phase | 2 mo. | Before therapy |
| | | | 31 | | | Fifth day of period of electric shock therapy |
| 37 | F | 25 | 35 | Manic depressive psychosis, mixed (discharged) | 4 yr. | First day of period of electric shock therapy |
| | | | 35 | | | Fourth day of period of electric shock therapy |
| | | | 40 | | | Seventeenth day of period of electric shock therapy |
| 38 | F | 26 | 37 | Schizophrenia, catatonic (discharged; post partum) | 2 mo. | Sixtieth day of period of insulin therapy |
| 39 | F | 32 | 33 | Schizophrenia, paranoid | 8 yr. | |
| 40 | F | 50 | 47 | Schizophrenia, paranoid | 3 yr. | |
| 41 | F | 62 | 40 | Involutional psychosis, melancholia (discharged) | 2 mo. | Before therapy |
| | | | 21 | | | Eleventh day of period of electric shock therapy |
| 42 | F | 76 | 66 | Senile psychosis | 6 yr. | Before therapy |
| | | | 53 | | | Sixth day of a period of electric shock therapy |
| 43 | F | 27 | 78 | Manic-depressive psychosis, manic phase | 10 yr. | |
| 44 | F | 66 | 28 | Involutional psychosis, melancholia (discharged) | 1 mo. | Before therapy |
| | | | 20 | | | Seventh day of period of electric shock therapy |
| 45 | F | 57 | 66 | Involutional psychosis, melancholia (discharged) | 6 mo. | Before therapy |
| | | | 50 | | | Six hours after first electric shock |
| | | | 54 | | | Fifteenth day of period of electric shock therapy (discharged) |
| 46 | F | 43 | 15 | Schizophrenia, paranoid | 2 yr. | |
| 47 | F | 51 | 28 | Involutional psychosis, melancholia (discharged) | 18 mo. | Before therapy |
| | | | 38 | | | First day after first electric shock |
| | | | 38 | | | Twelfth day of period of electric shock therapy |
| 48 | F | 32 | 29 | Schizophrenia, hebephrenic | 10 yr. | Eighteen months after leukotomy |
| 49 | F | 27 | 75 | Schizophrenia, hebephrenic | 13 yr. | |
| 50 | F | 54 | 78 | Schizophrenia, paranoid | 5 yr. | Two years after leukotomy |
| 51 | F | 50 | 112 | Involutional psychosis, paranoid | 3 yr. | |

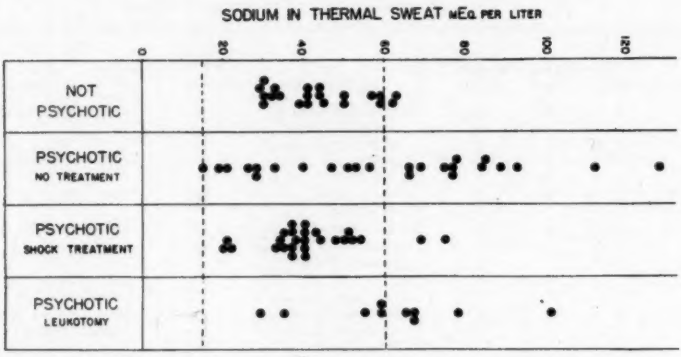


Chart 1.—Sodium concentration of thermal sweat in nonpsychotic and in psychotic subjects. The dotted lines indicate the normal range as reported by Conn.[8]

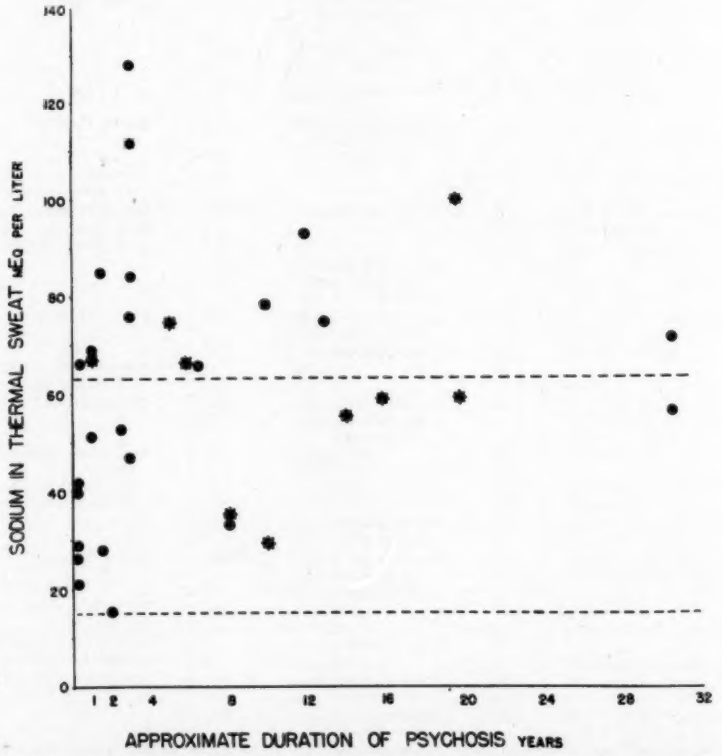


Chart 2.—Relation of sodium concentration of thermal sweat to duration of psychosis. The crenelated dots indicate patients with leukotomy; the dotted lines, the normal range found in the present study.

were above the highest normal level (table 2; charts 1 and 2). Of the 12 psychotic patients ill longer than three years, 9 showed sweat sodium concentrations above the normal range (chart 2). Determinations on patients after leukotomy revealed a range of 28 to 100 milliequivalents (chart 1), but the distribution was slightly different than that for the nonleukotomized patients. Of the 8 leukotomized patients ill longer than three years, sweat sodium concentrations were above the normal range for only 3 (cases 30, 39 and 50, table 2). The sweat sodium concentration could not be correlated with diagnostic categories (table 2).

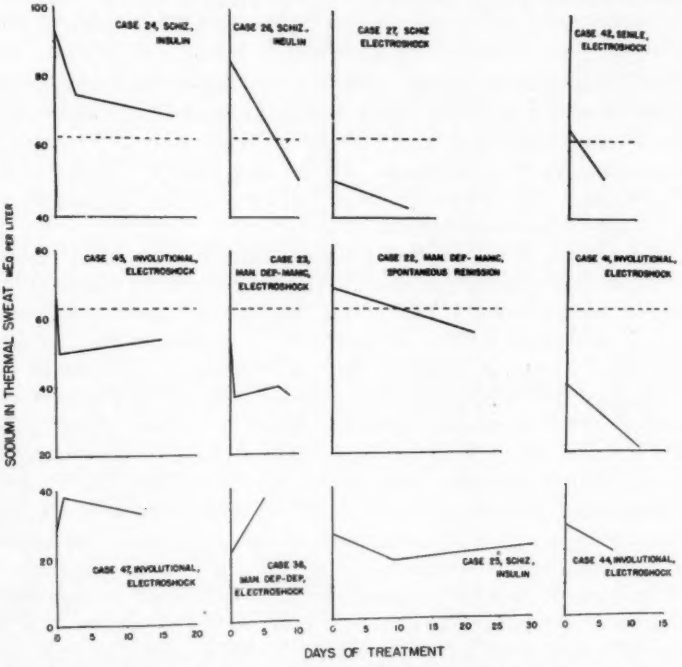


Chart 3.—Effect of therapy on sodium concentration of thermal sweat. The dotted lines indicate the upper normal limit found in the present study.

After electric convulsion or subcoma insulin therapy, a fall occurred in the sweat sodium concentration of patients whose original levels were above the normal range (cases 24, 26, 42 and 45, table 2; charts 1 and 3). This decrease ranged from 12 to 34 milliequivalents, with an average of 20 milliequivalents. One patient who recovered spontaneously showed a similar change (case 22, table 2; chart 3). Patients in whom normal sweat sodium concentrations were found before treatment showed variable changes after treatment, 5 of the 7 showing decreases

(cases 23, 25, 27, 41 and 42, table 2) and 2 exhibiting increases (cases 36 and 47, table 2); for none after treatment were values outside the normal range (table 2; charts 1 and 3). Determinations made after many shocks revealed that the sweat sodium concentration, once down, remained at the same lowered level over the entire course of treatment (cases 18, 21, 23, 25, 37 and 45, table 2; chart 3). The fall in sweat sodium concentration was rapid, as evidenced by the fact that measurements made six hours after the first electric shock treatment showed the maximal decreases for those patients and further shocks had no additional effect (cases 23 and 45, table 2; chart 3).

## COMMENT

The nonpsychotic subjects studied here showed sweat sodium concentrations which compared closely with those reported by Conn,[3] whose normal values ranged from 15 to 60 milliequivalents. The normal subjects described by Fitzhugh, Moseley and Merrill[4] showed values which ranged from 15 to 92 milliequivalents. These differences are due possibly to different methods of collection.

The results of the present study indicate that the sweat sodium concentration of psychotic patients is frequently above the normal range,[5] and that when elevated it falls during treatment or spontaneous remission. If the sweat sodium concentration is a measure of activity of the adrenal cortex, as suggested by Conn,[3] it must be concluded that chronic psychosis is frequently accompanied with evidence of decreased secretion of the electrolyte-regulating hormone of the adrenal gland, and that electric shock, insulin and spontaneous remission cause increased secretion of that hormone. This study indicates, further, that when the psychosis has been present continuously for three years or more, most patients have evidence of impairment of this function of the adrenal gland, irrespective of diagnosis. On the other hand, psychosis of shorter duration may be associated with either normal or high sweat sodium concentrations; this does not rule out the possibility that the hormonal change considered responsible for the abnormal findings may be present in latent form or mild degree in patients with normal sweat sodium concentration. It is not clear whether the apparent change in

3. Conn, J. W.: Electrolyte Composition of Sweat: Clinical Implications as an Index of Adrenal Cortical Function, Arch. Int. Med. **83**:416 (April) 1948.

4. Fitzhugh, F. W.; Moseley, A. J., and Merrill, A. J.: Sweat Sodium Concentration in Thyrotoxicosis, J. Clin. Investigation **28**:781, 1949.

5. The fact that Edelmann and associates (Edelmann, A.; Makanna, D. L.; Lewis, L. A.; Thatcher, J. S., and Hartman, F. A.: Use of Adrenal Extract in Fever Therapy, J. Clin. Endocrinol. **3**:20, 1943) found sweat sodium concentrations of 84 to 144 milliequivalents in patients with cerebral syphilis is difficult to relate to the results of the present study, for these authors collected sweat during induced fevers, with temperatures of 105 to 106 F. lasting over three hours.

function of the adrenal cortex bears a specific relation to chronic psychosis or whether it is a change common to prolonged illnesses in general. The observed disorder of electrolyte regulation cannot be severe in degree, for none of the patients studied here showed abnormal plasma sodium or potassium levels.

The effect of shock therapy in stimulating the adrenal gland, and so causing a fall in sweat sodium concentrations, accords with observations on the fall of eosinophils and lymphocytes and the decrease in the uric acid–creatinine ratio.[1a-f] The change in electrolytes is probably due to the 11-desoxycorticosterones, and the changes in eosinophil and lymphocyte counts and the uric acid content are due to the 11-oxycorticosterones. The occurrence of a decrease in sodium in the sweat in a psychotic patient who made a spontaneous recovery (case 22) may also have been related to stimulation of the adrenal cortex, for it has been shown that stressful psychiatric interviews cause changes indicative of increased adrenal cortex activity.[6]

Increased production of electrolyte-regulating hormone during treatment leads to sodium retention and consequently results in an increase in the volume of extracellular fluid, as observed previously.[1g-j] The increased production of this hormone also accounts for the effect of treatment in accelerating the delayed water diuresis in psychosis.[1k]

The effect of leukotomy on the sweat sodium concentration is not sufficiently clear to permit any conclusions. It is possible that some change in adrenal function may occur after leukotomy, since this operation in women is followed by a decrease in excretion of the 17-ketosteroid hormone.[7] Perhaps it is significant that several patients with long-term psychoses who had had leukotomies had normal sweat sodium concentrations, indicating normal electrolyte-regulating hormonal function.

The relation of the sweat sodium concentration to clinical status is variable. Some psychotic patients have normal values before treatment, while for others therapy may result in a decrease to a normal value without remission of the psychosis. It is evident, therefore, that increased production of the electrolyte-regulating hormone by the adrenal cortex does not in itself give rise to the beneficial effects of shock therapy, but appears to be an index of the stimulation of the adrenal cortex which occurs during treatment. On the other hand, all patients who improved sufficiently to be discharged had normal sweat sodium concentrations as a consequence of therapy or of spontaneous remission.

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6. Shands, H. C., and Finesinger, J. E.: Lymphocytes in the Psychoneuroses: Preliminary Observations, Am. J. Psychiat. **105**:277, 1948.

7. Reitman, F.: Steroid Metabolism and the Frontal Lobes, Brit. M. J. **1**:1064, 1948.

## SUMMARY AND CONCLUSIONS

The range of sweat sodium concentrations is above the normal for most psychotic patients, irrespective of their clinical diagnoses, who have been ill for more than three years. Patients ill for shorter periods may show either normal or high values. Increased sweat sodium concentrations fall to normal during insulin therapy, electric shock therapy and spontaneous remission. These observations suggest that diminished production of hormones controlling the electrolyte balance is frequent in psychosis and that treatment stimulates production of these hormones. These findings support other evidence which suggests that abnormal function of the adrenal cortex may occur in mental disease. On the other hand, the data show clearly that increased production of the electrolyte-regulating hormone is not the cause of clinical improvement in patients receiving shock treatment.

Dr. I. Taylor, of Harvard Medical School, assisted in the performance of the analysis.

# WEAKNESS OF EXTENSOR MUSCLES OF THE WRIST

## An Early Sign in Hemiparesis

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IN A RECENT issue of the *Journal of the Medical Society of New Jersey,* Dr. Samuel A. Sandler[1] has written an article entitled "Depression Masking Organic Diseases and Organic Diseases Masking Depression." In 1 of the cases in this article, he mentions the presence of the Strauss sign. I have not described this sign in a published article, although it is known and used by many of my associates. Therefore, I wish to record this sign.

It not infrequently happens that the internist, even the neurologist, has a case in which he suspects a condition of hemiparesis and yet there does not seem to him to be a sufficient loss of power in the limbs on the suspected side to warrant this diagnosis. This even occurs sometimes when the reflexes on the suspected side of the body are greater than those on the other or the abdominal skin reflexes are absent; there may even be indications of pathologic reflexes, such as the Babinski sign. In testing the muscle power of the hands, the grip, and the other flexor muscles of the arm or even of the leg the examiner finds no obvious loss of power. In such cases, I have found not infrequently that if the physician will have the patient extend the hands at the wrist on the side suspected of paresis and then with the palm of his own hand press down and ask the patient to resist him he will find that on the side suspected of being affected, the wrist muscles will give way slowly or suddenly and the hand will drop. For comparison, he should try the same procedure on the opposite side; he will find from it that it is with great difficulty that he can cause flexion of the wrist. This weakness of the extensor muscles of the wrist on the suspected side is definite evidence of a hemiparetic state and may even be the first and earliest sign of the development of the outspoken paresis of that half of the body.

I have found this sign frequently to be of great importance in differential diagnosis of cerebral conditions. There is a phylogenetic basis tor the early involvement of the extensors of the wrist. The flexors of the fingers and of the wrist dominate the extensors. This is not so empirically. Flexion of these joints is older phylogenetically. The posture of the hand in the primates is one of flexion. The gorilla or orang-

1. Sandler, S. A.: J. M. Soc. New Jersey **45**:108-110 (March) 1948.

utan has long forelimbs and short hindlimbs. He walks on the outer border of the foot with the big toe dorsiflexed. Because his heavy torso cannot be supported on this weak foundation, he stoops forward, his forelimbs thus also supporting the body. However, only the dorsum of the hand comes into contact with the ground as he goes forward. The posture of the hands is one of marked flexion in all the joints of the phalanges and at the wrist.

In the course of evolution, man has assumed the erect posture. Instead of walking on the outer border of the foot, he walks on the sole. The big toe, instead of being dorsiflexed, has become plantarflexed. It acts as a fulcrum on which is supported the weight of the entire body. The hand is only mildly flexed at all joints. Simultaneously with this assumption of erect posture and alterations in muscles, bones and joints, the corticospinal tract has attained its greatest development. Included in the newer functions of the corticospinal tract are maintenance of erect posture and volitional motor power.

Diseases of the corticospinal tract thus result in loss or impairment of voluntary motor power, increased deep reflexes, alterations of muscle tonus and presence of the Babinski toe sign. The posture of the hands and feet reverts to that present in the normal primate. The foot assumes the appearance designated as pes equinovarus, and the hand assumes the degree of flexion usually observed in hemiplegia. Among the earliest evidences of lessened functional activity of the corticospinal tract is impaired innervation of the more recently acquired muscular functions. One of the weakest links is the ability to maintain the hand dorsiflexed at the wrist. The presence of minimal corticospinal damage can thus be determined by the clinical test which has been described.

116 West Fifty-Ninth Street (19).

# CENTRAL PROTRUSION OF CERVICAL INTERVERTEBRAL DISK INVOLVING DESCENDING TRIGEMINAL TRACT

## Report of a Case

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LATERAL protrusion of a lower cervical intervertebral disk has been thoroughly investigated by recent workers, and its pressure effect on the nerve root has become a distinct clinical syndrome. However, protrusion occurring in the midline, compressing chiefly the spinal cord, has often been mistaken for neoplasm, as is well illustrated by the early writings of Stookey [1] and Dandy.[2] It is the purpose of this paper not only to point out once more that central protrusion of a cervical intervertebral disk may give rise to symptoms simulating tumor of the cord, syringomyelia or syringobulbia, angina pectoris or sometimes even multiple sclerosis or amyotrophic lateral sclerosis, but to report a case in which there was involvement of the descending tract of the trigeminal nerve, a condition which to our knowledge has never before been reported.

### REPORT OF CASE

*History.*—J. E. C., a man aged 57, was admitted to the Montreal Neurological Institute on March 25, 1949, with the following complaints: (1) tingling in the tips of all the fingers for one year; (2) numbness and weakness in both hands for eight months; (3) pins and needles sensation in the shoulders and hands for six months; (4) brief episodes of dizziness on turning in bed or on rapidly changing position, of four months' duration, and (5) pain in the back of the neck and radiating to the tips of the fingers of both hands, produced by coughing on the day prior to admission.

The patient had been in fairly good health until 1942, when he fell from a scaffold a distance of 7 feet (2 meters). He landed on hands and feet and sustained a fracture of the right patella. After the accident he experienced no pain or discomfort in his neck, shoulders or arms.

In February 1947 he had sudden onset of precordial pain, for which he was admitted to the Queen Mary Veteran's Hospital. The diagnosis of repetitive auricular paroxysmal tachycardia and anxiety neurosis was made. Because of recurrent precordial pain and "anxiety neurosis," he was away from work for

1. Stookey, B.: Compression of Spinal Cord and Nerve Roots by Herniation of the Nucleus Pulposus in Cervical Region, Arch. Surg. **40**:417 (March) 1940.

2. Dandy, W. E.: Loose Cartilage from Intervertebral Disk Simulating Tumor of the Spinal Cord, Arch. Surg. **19**:660 (Oct.) 1929.

twelve months, during which period he was regularly observed at the clinic for cardiac disease. For ten months preceding the present admission he had been free from precordial pain.

In February 1948 he began to experience a sensation of tingling in all the fingers of both hands. Subsequently tingling occurred in the arms. This symptom came on at any time of the day and was not related to movement. Three months after its onset the tingling increased in severity and was described as a painful pins and needles sensation which persisted day and night. In addition, there had been periods of numbness in which the patient said his hands seemed to go to sleep. However, he had never burnt his fingers with cigarets. Six months later this sensation began to ascend, involving both shoulders.

In July 1948 the patient's wife died of "cirrhosis of the liver." He was then obliged to prepare his own meals. Frequently he broke glasses and dropped dishes. At first he blamed this on the lack of experience and practice, but later he was struck by the fact that he also dropped his cigarets. He soon realized that his hands were clumsy and weak. On admission he described his hands as "useless."

Since December 1948 he had had brief episodes of dizziness on turning in bed or on rapidly changing position. These episodes occurred four to six times a day, lasting for a period of a minute, and consisted of momentary blurring of vision, followed by a sensation of spinning of the head rather than of objects. These episodes had not been accompanied with nausea or vomiting, and at no time had the patient experienced ringing in the ears.

On the day before admission he noticed that when he coughed there was a sharp pain in the back of his neck, shooting down to all his fingers.

*Examination.*—General physical examination revealed a blood pressure of 150 systolic and 90 diastolic and regular pulse, with a rate of 80 beats per minute. The heart was not enlarged and was without murmurs. Movements of the neck were limited in all directions, especially in flexion. No cervical tenderness could be elicited.

Neurologic examination revealed a psychologically well balanced person, of average intelligence. Olfaction was normal bilaterally. Visual acuity was 20/20 with correction in each eye. The visual fields were full in all quadrants. Examination revealed a slight increase of refractility and narrowing of the retinal arterioles, with no hemorrhages or papilledema. There were ptosis and miosis of the left eye. The extraocular movements were normal; there was no nystagmus. Corneal sensation and corneal reflexes were absent on both sides. There was a circular area of anesthesia to touch, pain, heat and cold about 3 to 4 cm. in diameter over each cheek. A similar area of anesthesia, including the whole anterior one half to one third of the trigeminal area of the tongue, was found (fig. 1). Taste sense was well preserved. Sensation for all modalities over the rest of the face, including the nose and the lips, was normal. The motor component of the trigeminal nerve was intact bilaterally. There was no facial weakness. Acuity of hearing was slightly diminished, but air conduction was greater than bone conduction bilaterally. No abnormality in the function of the ninth, tenth, eleventh or twelfth cranial nerves was observed.

Fine fasciculations were noted in all muscle groups of the arms and the forearms, with sparing of the deltoid muscles. They were most marked in the triceps brachialis and were occasionally seen in the thenar and hypothenar muscles of both hands. Fasciculations were also observed in the adductor muscles and the quadriceps femoris of the lower extremities.

The patient was right handed. The circumference of the right arm measured 26 cm., and that of the left, 25 cm. The muscles of the arm appeared small as

compared with the deltoid. There was obvious wasting of the muscles of the forearms, particularly of the flexors, and of the small muscles of the hands. Weakness was present in all muscles but was greatest in the right triceps and in the distal groups. Atrophy and weakness, however, were not found in the lower extremities.

The biceps reflex was absent bilaterally. The radial reflex was absent on the right and diminished on the left. The triceps and ulnar reflexes were hyperactive and were equal on the two sides. The tendon reflexes of the lower extremities were hyperactive, with the patellar reflex and ankle clonus present bilaterally. Hoffmann and Chaddock signs were present bilaterally, and a Babinski reflex was elicited on the left side. The plantar response was equivocal on the right side. The abdominal reflexes were less active on the left than the right.

There was marked impairment of sensibility for pain, cold and warmth from the level of the nipple downward, with sparing of the sacral dermatomes on the right. A "glove type" of impairment of sensibility to touch, pain and thermal stimuli was found in the hands, gradually fading off at the level of the elbows. Two point discrimination was absent in the fingers of both hands and in the toes and the sole of the right foot. Vibration sense was not appreciated below the elbow

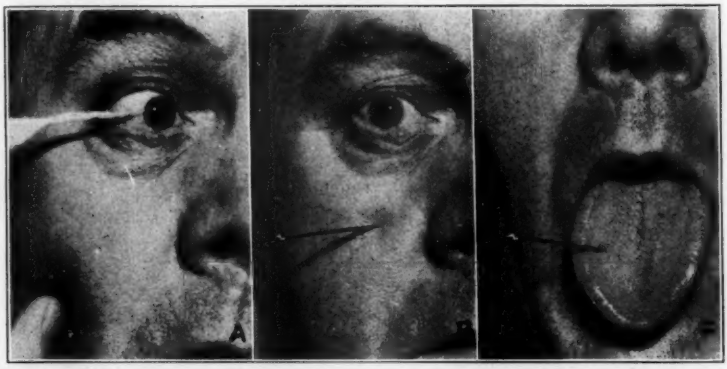

Fig. 1.—*A*, loss of corneal sensation and corneal reflex; *B*, loss of sensibility to all modalities over the cheeks; *C*, loss of sensibility to touch, pain and thermal stimuli in the anterior portion of the trigeminal area of the tongue, with preservation of taste sense.

in the upper extremities. It was faintly perceived over the lower ribs and ilium on the right side and was completely absent in the right leg. Position sense was absent in the fingers and the wrists on both sides and in the toes on the right side (fig. 2). Although the hands were clumsy, there was no disturbance of movement in the upper or lower limbs.

Laboratory data revealed normal urine and negative Kahn and Wassermann reactions of the blood. The hemogram was normal. The cerebrospinal fluid contained 103 mg. of protein per hundred cubic centimeters and 1 monocyte per cubic millimeter. The lumbar manometric test showed an initial pressure of 185 mm. of water and a partial subarachnoid block.

A roentgenogram of the chest disclosed no cardiac enlargement and no evidence of intrathoracic abnormality. Roentgenograms of the skull showed a normal condition except for bilateral sclerosis of the mastoid cells. Roentgenograms of the spine revealed pronounced osteoarthritis of the fifth, sixth and seventh cervical vertebrae with loss of disk spacing of these levels (fig. 3).

Myelographic examination showed a filling defect from the lower border of the third to that of the fifth cervical vertebra. This simulated the silhouette of a tumor, but the roentgenologist expressed the belief that it represented lack of filling due to technical reasons or, at the most, arachnoidal adhesions (fig. 3).

Summary: This patient had (1) a partial Horner syndrome on the left side; (2) loss of corneal sensation and corneal reflex on both sides, and anesthesia of both cheeks and of the anterior one half to one third of the trigeminal area of

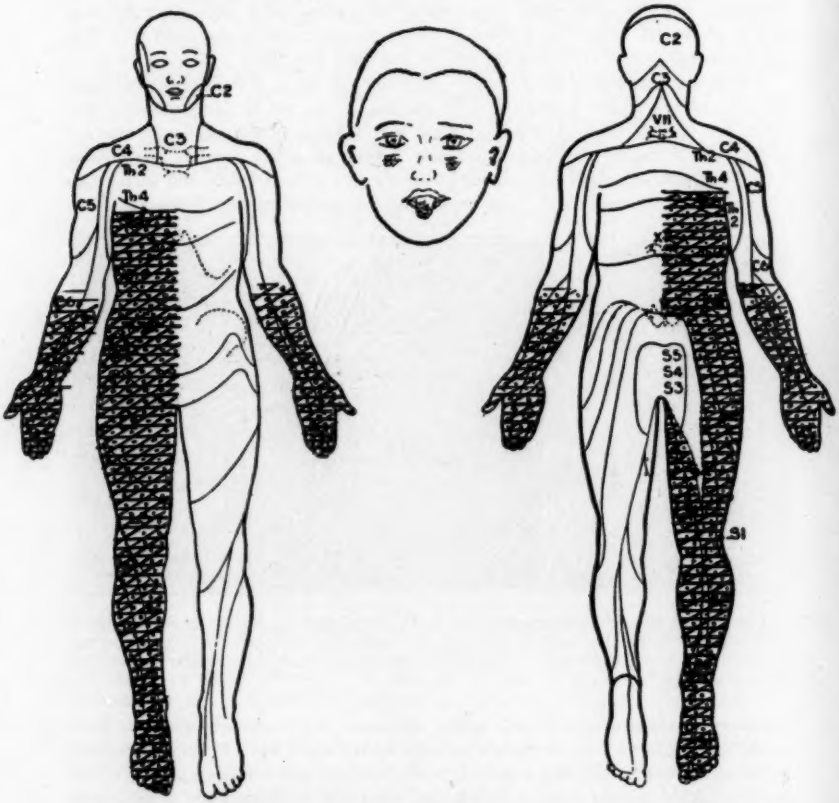


Fig. 2.—Sensory changes. Dots indicate impairment of tactile sense; diagonal lines, impairment of pain perception, and horizontal lines, impairment of thermal sensibility.

Two point sensation was absent in the fingers of both hands and in the toes and the sole of the right foot; vibration sensation was absent in the hands and in the right leg; position sensation was absent in the hands and in the toes of the right foot.

the tongue; (3) a sensory level for pain, heat and cold at the level of the fourth thoracic segment on the right side with sacral sparing; loss of two point discrimination, position and vibration sensation in the hands and in the right foot, and a glove type of anesthesia in both hands; (4) fasciculations, muscular atrophy

and weakness in the upper extremities; (5) absence of the biceps reflex on both sides and of the right radial reflex; bilateral Hoffmann sign, patellar reflex and ankle clonus, and depressed abdominal reflex and extensor plantar response on the left side; (6) increased protein content of the cerebrospinal fluid and partial lumbar manometric block; (7) osteoarthritic changes in the fifth, sixth and seventh cervical vertebrae, and, finally, (8) inadequate filling of the subarachnoid space by pantopaque® from the level of the third cervical vertebra to that of the fifth.

The differential diagnosis lay between intramedullary or extramedullary tumor and ruptured cervical intervertebral disk; the former diagnosis was supported by the bizarre neurologic findings, while the latter was based on the history and the myelographic evidence. Syringomyelia or syringobulbia was also suggested. In any case, exploration was planned.

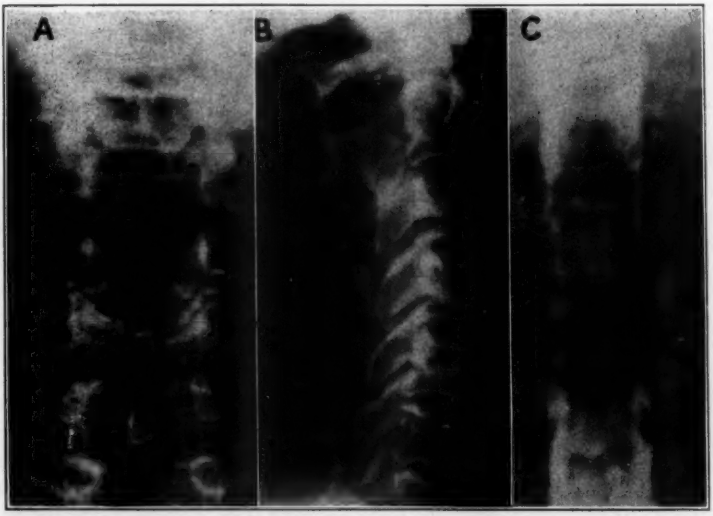


Fig. 3.—Roentgenograms of the cervical portion of the spine: *A*, anteroposterior view; *B*, lateral view. *C* is a myelogram of the cervical region.

On April 1, bilateral laminectomy from the third to the sixth cervical vertebra was performed. The dura appeared to be under tension, and there was some overall backward displacement. On neither side, however, was anything abnormal seen laterally. The dura was opened. The arachnoid was slightly thicker and more opalescent than usual, and there were many fine adhesions between the dura and the arachnoid, which had to be peeled off from the dura. In addition, there seemed to be some delicate subarachnoidal loculations, since separate gushes of fluid occurred when various portions of the arachnoid were opened. On one occasion, on exploration anteriorly, it seemed as though a very small amount of slightly yellowish fluid was obtained.

The spinal cord itself was of normal color and consistency. It did not appear enlarged but was displaced somewhat backward at the level of the fourth and fifth cervical vertebrae. Two slips of the dentate ligaments were sectioned at the levels of the third, fourth and fifth cervical segments bilaterally. Exploration revealed,

anterior to the spinal cord, a protrusion of the disk between the fourth and fifth cervical vertebrae near the midline extending toward the left side and also, to a much lesser extent, toward the right. The protrusion was about 3 or 4 mm. in height at the midline, and its base spread on to the adjacent vertebral bodies. It was almost impossible to approach it extradurally, as it was medial to a well marked natural lateral gutter. The dura, therefore, was incised anteriorly just adjacent and medial to the lateral gutter. Through this, small amounts of disk were squeezed out and removed. A small dissector was then passed extradurally into the cavity. Extradural removal was then made with simultaneous intradural manipulation. A similar procedure was carried out on the opposite side, so that finally a through and through removal of the disk was made, and the articular surfaces of the adjacent bodies were scraped with a small curet. After the removal the spinal cord seemed to have relaxed. The nerve roots on both sides appeared to have sufficient room, but a considerable amount of bone from over

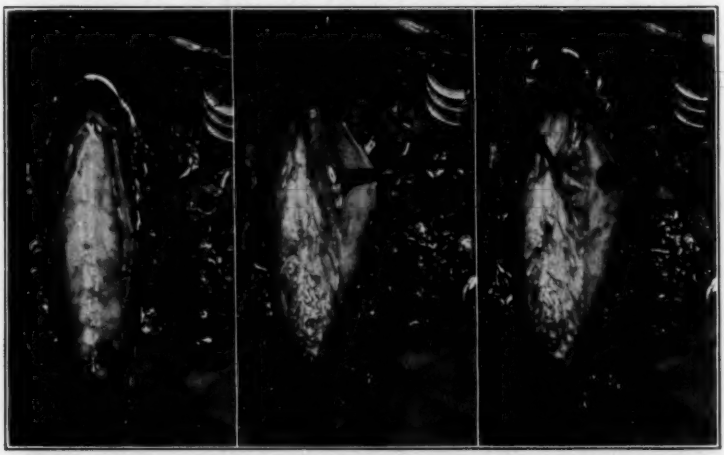

Fig. 4.—*A*, thickening and opalescence of the arachnoid, subarachnoidal loculations and backward displacement and stretching of the cord; *B* extradural protrusion of the intervertebral disk revealed by anterior exploration; *C*, incision of the anterior portion of the dura and extradural removal with simultaneous intradural manipulation.

the nerve root was removed in order to achieve further decompression. The dura was then repaired and the operative wound closed (fig. 4).

Three hours after the operation the patient moved all extremities but complained of pain, like a toothache, about his shoulders. There was less sensation of the pins and needles type in the arms. The Horner syndrome on the left remained unchanged, and the objective sensory changes were the same as those found before the operation. However, the patellar reflex and ankle clonus had disappeared.

On the first postoperative day a cough developed. However, this no longer caused pain to radiate down his arms. Dizziness, which prior to operation occurred on his turning, was no longer experienced.

On the second postoperative day the corneal reflex and the sensibility over the face and tongue had returned to normal on both sides. The glove type of anesthesia had rolled down to the wrists. Position and vibration sense and two

point discrimination had returned in the fingers and in the toes of his foot. The hand grip, as registered by the dynamometer, was 60 pounds (27 Kg.) on the right and 40 pounds (18 Kg.) on the left, readings which were almost twice the previous records.

The patient continued to improve. He was up and about, with a felt collar, two weeks after the operation, and he was discharged on the twenty-fourth postoperative day.

On May 10, forty days after the operation, the patient stated that he still had occasional numbness and tingling in the fingers and hands. He no longer dropped his cigarets, and his hand grips were as strong as those of the examiner. However, fine fasciculations were still visible in the upper limbs. The plantar response was still extensor on the left side. There was still a sensory level at the fourth thoracic dermatome on the right with sacral sparing; this, however, could be obtained only by careful examination; in fact, it had escaped the notice of the first examiner. On the other hand, the Horner syndrome on the left had entirely disappeared; the corneal reflex was brisk on both sides, and the cheeks and the tongue were normally sensitive.

## COMMENT

It is interesting to note that this patient had been under the treatment of a cardiologist for twelve months and had been considered neurotic. Semmes and Murphey,[3] in reporting 4 cases of protruded cervical intervertebral disk, stated the belief that "an undetermined number of patients with pain in the precordium . . . who heretofore were thought to have coronary thrombosis [or] angina pectoris . . . will be found to have a rupture of one of the lower cervical disks." In 1946 Josey and Murphey [4] further emphasized this syndrome in the differential diagnosis of coronary artery disease with a report on 7 cases. In 3 of their cases a previous diagnosis of heart disease had been made, and the patients had been treated for this condition. Three patients had manifestations of anxiety because of pain. During the operation Josey and Murphey were able to reproduce the patient's precordial pain by applying pressure to the protruded disk itself. However, the mechanism for the development of precordial pain in cases of protruded cervical intervertebral disk is still not clear. If the pain provoked from the disk itself is segmentally distributed, a bilateral distribution is more likely to occur, or there is pain on the right side of the chest when the protrusion is to the right of the midline. Furthermore, we have tried to duplicate Kellgren's [5] experiment by injecting hypertonic saline solution into the deep-lying structures at the first thoracic and seventh cervical, the sixth and seventh cervical, the sixth and fifth cervical and the fifth and fourth cervical vertebrae; no precordial pain or hyperalgesia was produced.

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3. Semmes, R. E., and Murphey, F.: The Syndrome of Unilateral Rupture of Sixth Cervical Intervertebral Disk, J. A. M. A. **121**:1209 (April 10) 1943.

4. Josey, A. I., and Murphey, F.: Ruptured Intervertebral Disk Simulating Angina Pectoris, J. A. M. A. **131**:581 (June 15) 1946.

5. Kellgren, J. H.: Somatic Simulating Visceral Pain, Clin. Sc. **4**:35, 1939.

Dizziness on turning and on rapid changes of position associated with protruded intervertebral cervical disk is difficult to explain. In a case reported by Alajouanine and Thurel [6] the patient swayed incessantly forward and backward when in the erect position. His gait was spastic and unsteady. Hypermetria was pronounced in the finger-nose test and in the heel-knee-tibia test. The myelogram disclosed a protrusion of the intervertebral disk between the fourth and fifth cervical vertebral bodies. After the removal of two fibrocartilaginous fragments, which were completely detached from the disk, symptoms progressively improved. However, Alajouanine and Thurel did not mention dizziness as one of the complaints of their patient. Tumors in the foramen magnum compressing the medulla are known to give rise to vestibulocerebellar disturbance, but this symptom has not hitherto been described in a case of protruded cervical disk or in cervical tumor.

It was found at operation that the cord was pushed backward as it passed over the protrusion of the disk between the fourth and fifth cervical vertebrae. There were many fine adhesions between the dura and the arachnoid. There were also subarachnoidal loculations. These associated findings may have been responsible in part for the bizarre clinical features. Barr and Mixter [7] pointed out that with intervertebral disk disease spinal arachnoiditis may be found. Of 200 patients operated on by French [8] for protruded intervertebral disk, 13 were found to have local arachnoiditis. In addition to the protruded disks, he noted "a thickened milky-appearing arachnoid with localized gross matting together by adhesions of the filament of the cauda equina. The process extended one to two segments above the protruded nucleus pulposus, and was frequently sufficiently marked to cause complete pantopaque obstruction well above the extradural compression." Most of his patients showed diffuse physical signs out of proportion to compression of a single root. Proteins in the cerebrospinal fluid were increased from 40 to 630 mg. per hundred cubic centimeters in 6 cases, and manometric block was present in 1 case.

Bony proliferation is rather common in cases of protruded intervertebral disk. The consistency of the extruded cartilaginous mass on palpation is, in fact, comparable to that of bone. That the irritation created by its constant rubbing on the cord or on the nerve root is greater than that resulting from a soft neoplasm is understandable. Being fixed to the spine, furthermore, its frictional effect on the con-

6. Alajouanine, T., and Thurel, R.: Hernie discale de la région cervicale: Quadriplégie cérébello-spasmodique simulant la sclérose en plaques, Rev. neurol. **79**:765, 1947.

7. Barr, J. S., and Mixter, W. J.: Posterior Protrusion of the Lumbar Intervertebral Discs, J. Bone & Joint Surg. **23**:444, 1941.

8. French, J. D.: Clinical Manifestation of Lumbar Spinal Arachnoiditis: Report of Thirteen Cases, Surgery **20**:718, 1946.

stantly moving cord or nerve root has a wider range than does that of a tumor arising from the dura or from the cord itself.

Finally, the effect of pressure on the anterior aspect of the spinal cord, which is anchored by the dentate ligament, may apparently be far greater than one would expect. A vascular mechanism from compression of the anterior spinal artery may be set in motion, giving rise to spasm, closure or thrombosis. Secondary changes with necrosis of the spinal cord had been reported by Dandy.[9]

Horner's syndrome has occasionally been observed in patients with protruded cervical intervertebral disk. We have seen a patient with protrusion between the sixth and the seventh cervical vertebra who showed a Horner syndrome on the right side, in association with a trophic change in the skin of the right hand. This must have been due to interruption of the sympathetic outflow to the limb, as well as to paralysis of the ciliospinal pathway. In the case here reported the ciliospinal fibers were involved.

There had been no previous report of involvement of the descending spinal tract of the trigeminal nerve in association with protrusion of the cervical intervertebral disk. With regard to how far this tract descends into the spinal cord various opinions are given in the literature. In the calf Gudden[10] claimed that this tract terminates at the level of the fifth cervical segment. In rabbits Bregmann[11] traced the degenerated fibers by the Marchi technic caudally to the level of the second cervical segment. This observation was confirmed by Wallenberg.[12] Gerard,[13] in her thesis, summarized work on this subject up to 1923 and, from her study of 21 cats, concluded that in this animal this tract does not descend beyond the first cervical segment. This conclusion was in agreement with the work of McKinley and Magoun,[14] who, in a study of the action potentials, found that spikes from the primary afferent fibers of the mandibular division were recorded as far caudally as the level of the obex, while maxillary and ophthalmic fibers were detected as far

9. Dandy, W. E.: Serious Complications of Ruptured Intervertebral Disks, J. A. M. A. **119**:474 (June 6) 1942.

10. Gudden, H.: Beitrag zur Kentniss der Wurtzeln des Trigeminus Nerven, Allg. Ztschr. f. Psychiat. **48**:16, 1892.

11. Bregmann, E.: Ueber experimentelle aufsteigende Degeneration motorischen und sensiblen Hirnnerven, Arb. a. d. Inst. f. Anat. u. Physiol. d. Centralnervensyst. an. d. Wien. Univ. **1**:73, 1892.

12. Wallenberg, A.: Die secondäre Bahn des sensiblen Trigeminus, Anat. Anz. **12**:95, 1896.

13. Gerard, M. W.: Afferent Impulses of the Trigeminal Nerve, Intramedullary Course of the Painful, Thermal and Tactile Impulses, Arch. Neurol. & Psychiat. **9**:306 (March) 1923.

14. McKinley, W. A., and Magoun, H. W.: The Bulbar Projection of the Trigeminal Nerve, Am. J. Physiol. **137**:217, 1942.

caudally as the first cervical segment. In monkeys Walker [15] was able to follow the degenerated fibers down to the level of the lower margin of the first cervical segment. In man Sjöqvist [16] demonstrated that the tract ends at the level of the first cervical segment. In a patient who died of a cardiac attack suddenly seventeen days after trigeminal rhizotomy, Dr. Hanbery, of this Institute, was able to trace the spinal tract to a level immediately above the entrance of the second posterior cervical root. Nevertheless, several recent textbooks state that the spinal tract of the trigeminal nerve can still be found at the second cervical segment.[17]

In the present state of knowledge, therefore, it would appear that the descending spinal tract of the trigeminal nerve in man descends to the level of the first, or, at the most, of the second, cervical segment. In the case reported here the sensory loss of the face must have been caused by a lesion extending to, or above, that level, or else one must assume that the spinal tract had extended down to, or beyond, the level between the fourth and the fifth vertebral body, where protrusion of the intervertebral disk had occurred.

There has been a great deal of discussion about the concentric distribution of the trigeminal representation within the pons, the medulla and the upper cervical portion of the cord. According to Smyth,[18] von Sölder (1899) and Schlesinger (1899, 1902) postulated that "the fibres from the fronto-cranial territory of the ophthalmic nerve terminated in the most caudal part of the spinal tract. The fibers of the mandibular nerve terminated at a slightly higher level and those from the maxillary nerve higher still. Finally the fibres from the nasal portion of the ophthalmic nerve terminated highest of all." Kutner and Kramer,[18] Dejerine [19] and Woods,[20] on the basis of clinical observations, arrived at similar conclusions. On the other hand, Bregmann,[11] Wallen-

15. Walker, A. E.: Origin, Course and Termination of Secondary Pathways of Trigeminal Nerve in Primates, J. Comp. Neurol. **71**:59, 1939.

16. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve: Contribution to Surgical Treatment of Facial Pain, Acta psychiat, et neurol., 1938, supp. 17, pp. 1-139.

17. Krieg, W. J. S.: Functional Neuroanatomy, Philadelphia, The Blakiston Company, 1942. Mettler, F. A.: Neuroanatomy, St. Louis, C. V. Mosby Company, 1942. Strong, O. S.: Human Neuroanatomy, Baltimore, Williams & Wilkins, 1943.

18. Smyth, G. E.: The Systemization and Central Connection of the Spinal Tract and Nucleus of the Trigeminal Nerve: A Clinical and Pathological Study, Brain **62**:41, 1939.

19. Dejerine, J.: Sémiologie des affections du système nerveux, Paris, Masson et Cie, 1914.

20. Woods, A. H.: Segmental Distribution of the Spinal Root and Nucleus of the Trigeminal Nerve, J. Nerv. & Ment. Dis. **40**:91, 1913.

berg [12] and Spiller [21] stated the belief that the representation in the descending tract was in terms of peripheral divisions. This view was supported by the work of Wyllie [22]; Taylor, Greenfield and Martin [23]; Sjöqvist,[16] and Smyth.[18] Recently it was further emphasized by Weinberger and Grant,[24] who studied 18 cases after trigeminal tractotomies in great detail. From oscillographic recordings of potentials evoked by stimulation of peripheral nerves in cats, McKinley and Magoun [14] also concluded that the representation in the spinal tract was in terms of peripheral divisions.

However, it is hard to deny that the "onion peel" arrangement of facial analgesia in cases of a lesion proceeding rostrad through the medulla does occasionally occur. In the present case corneal insensibility and complete loss of sensation over the cheeks and in the anterior portion of the trigeminal area of the tongue seemed to follow the "onion peel" pattern. According to Dejerine, these areas would fall into the first the second, or V5 and V4, layers representing the highest, or pontile, segment and the medullary segment. Thus, if one favors the "onion peel" hypothesis, one must conclude that the functional disturbance resulting from the protruded intervertebral (fourth-fifth cervical) disk extended to the bulb. At present there is no convincing explanation.

That the spinal tract is composed exclusively of fibers conducting painful and thermal sensations has been widely accepted (Hun,[25] Spiller,[26] Stopford,[27] Gerard,[13] Sjöqvist [16] and Smyth [18]). On the other hand, Walker [28]; Grant, Groff and Lewy,[29] and Weinberger and Grant [24] have demonstrated diminution of tactile sensitivity after intramedullary trigeminal tractotomy. The slight diminution, as pointed out by these

21. Spiller, W. G.: The Symptom Complex of Occlusion of the Posterior Inferior Cerebellar Artery: Two Cases with Necropsy, J. Nerv. & Ment. Dis. **35**:365, 1908.

22. Wyllie, W. G.: Unilateral Bulbar Lesion, Probably Syringobulbia, with Special Reference to Sensory Pathways Within Medulla, J. Neurol. & Psychopath. **4**:148, 1923.

23. Taylor, J.; Greenfield, J. G., and Martin, J. P.: Two Cases of Syringomyelia and Syringobulbia, Observed Clinically over Many Years, and Examined Pathologically, Brain **45**:323, 1922.

24. Weinberger, L. M., and Grant, F. C.: Experiences with Intramedullary Tractotomy: Studies in Sensation, Arch. Neurol. & Psychiat. **48**:355 (Sept.) 1942.

25. Hun, H.: Analgesia, Thermic Anaesthesia and Ataxia, New York M. J. **65**:613, 1897.

26. Spiller, W. G.: Remarks on the Central Representation of Sensation, J. Nerv. & Ment. Dis. **42**:399, 1915.

27. Stopford, J. S. B.: The Function of the Spinal Nucleus of the Trigeminal Nerve, J. Anat. **59**:120, 1924.

28. Walker, A. E.: Anatomy, Physiology and Surgical Considerations of Trigeminal Nerve, J. Neurophysiol. **2**:234, 1939.

29. Grant, F. C.; and Groff, R. A., and Lewy, F. H.: Section of the Descending Root of the Trigeminal Nerve, Arch. Neurol. & Psychiat. **43**:498 (March) 1940.

investigators, could not be detected with cotton wool, but was demonstrated by von Frey hairs. However, the value of this method for the examination of light touch has been controversial. Smyth [18] stated that "if the sense of touch be tested with von Frey's hairs it is found that the lightest contacts are readily perceived." In our case tactile sensitivity was absent, and we used cotton.

Objective sensory and motor signs resembling the Brown-Séquard syndrome are common in cases of neoplasm of the spinal cord and are occasionally observed in patients with protruded cervical intervertebral disk.[30] However, bilateral weakness, atrophy and fasciculations in association with protruded cervical disk are rare. Physical findings suggestive of amyotrophic lateral sclerosis and multiple sclerosis were described by Alajouanine and Thurel.[31] Recently Kahn,[32] Meyer and Fine [33] reported similar cases.

The glove type of anesthesia, together with muscular atrophy, is commonly seen in cases of peripheral neuritis and syringomyelia. With the latter disease sensory dissociation is also found. While dermatomal distribution of hypalgesia is almost invariably obtained with lateral protrusion of the cervical disk,[34] this form of sensory change is not likely to be present in association with central protrusion of the cervical disk, which compresses chiefly the spinal cord.

## CONCLUSION AND SUMMARY

A case of central protrusion of a cervical intervertebral disk is reported.

The clinical symptoms and physical signs, which may mimic those of tumor of the spinal cord, angina pectoris, syringomyelia, syringobulbia, multiple sclerosis and lateral sclerosis, are discussed.

Involvement of the spinal tract of the trigeminal nerve in association with protrusion of a cervical intervertebral disk, which has never before been reported, was present in our case. The caudal limit of the descending tract, its central representation and the presence of tactile conducting fibers are discussed.

Montreal Neurological Institute.

30. Stookey.[1] Elsberg, A.: The Extradural Ventral Chondroma (Ecchondroses): Their Favorite Sites, the Spinal Cord and Root Symptoms They Produced, and Their Surgical Treatment, Bull. Neurol. Inst. New York **1**:350, 1931.

31. Alajouanine, T., and Thurel, R.: Hernie discale de la région cervicale, Rev. neurol. **78**:53, 1946.

32. Kahn, E. A.: The Role of the Dentate Ligaments in Spinal Cord Compression: Another Syndrome of Lateral Sclerosis, J. Neurosurg. **4**:191, 1947.

33. Meyer, B. C., and Fine, B. D.: Atypical Syndromes Produced by Extramedullary Tumor of Cervical Portion of Spinal Cord, Arch. Neurol. & Psychiat. **61**:262 (March) 1949.

34. Keegan, J. J.: Dermatome Hypalgesia with Posterolateral Herniation of Lower Cervical Intervertebral Disc, J. Neurosurg. **4**:115, 1947.

# DIGITAL EXTENSION REFLEX

## A Preliminary Communication

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IN THE course of a systematic investigation of the behavior and reflexes of the newborn infant, I observed a reflex which to my knowledge has not been specifically described in the literature up to now. A total of 145 newborn infants were examined by us, of which 17 (8 boys and 9 girls) were studied within the first twelve hours after birth.

A total of 624 tests were applied to these 145 children. To insure the possibility of an exact check of the whole testing procedure, motion pictures were taken of the behavior of each of the 145 subjects before, during and after the tests for the purpose of ultimate screen analysis.[1]

Reports on our observations in the different sectors of the personality of the newborn infant have been published elsewhere.[2]

In the course of these observations, it was found that, while palmar stimulation of the hand elicits reflex grasping, dorsal stimulation of the hand elicits an extensor reaction of the fingers and hand. However, this experiment could not be made (for accidental reasons) in 29 of the cases which I observed. The distribution of the cases in which the digital extension reflex was investigated is shown in table 2.

In the reflex activity of the hand a stretching of the fingers in response to palmar stimulation is never observed. The very careful investigation made by Halverson[3] showed that in a large majority of cases palmar stimulation results in a grasping reaction. Light cutaneous stimulation was differentiated by him from deep tendon stimulation. The latter was found more reliable in eliciting the grasping reflex than the former. Both types of stimulation showed a certain measure

1. In the year 1935, I introduced as a routine procedure for my investigation the taking of motion pictures at a speed of 24 frames a second. Since the movement of the film can be slowed down during projection to 8 frames a second, the speed of 24 a second insures the possibility of observing the subjects' behavior in slow motion at a rate three times as slow as it actually took place—in other words, at a magnification of 3 times. I called this procedure "screen analysis."

2. Spitz, R. A.: Emotional Growth in the First Year, Child Study **24**:68, 1947; The First Fifteen Minutes of Life, Motion Picture Available at New York University Film Library.

3. Halverson, H. M.: Studies of the Grasping Responses of Early Infancy, J. Genet.-Psychol. **51**:393 (Dec.) 1937.

of the unreliability characteristic of the reflexes of newborn infants in general; but neither of the two stimulations would elicit extension of the fingers.

The stimulus offered in my experiment consisted in gentle stroking, applied on the dorsal surface of the end phalanx of the four fingers simultaneously. No pressure was exerted. Care was taken to apply the stimulus at a moment when no "forced grasping" was taking place

TABLE 1.—*Number of Newborn Infants Tested and Filmed—for Early Reflexes*

| Time of Testing | Number of Infants | | |
|---|---|---|---|
| | Male | Female | Total |
| Within first week | 33 | 32 | 65 |
| After first week | 37 | 43 | 80 |
| Total | 70 | 75 | 145 |

TABLE 2.—*Distribution of the Digital Extension Reflex in a Group of Newborn Infants*

| | Number of Infants | | |
|---|---|---|---|
| | Male | Female | Total |
| Within first week of life | | | |
| Reflex present | 12 | 14 | 26 |
| Reflex absent | .. | .. | .. |
| Total | 12 | 14 | 26 |
| Second week or later | | | |
| Reflex present | 21 | 30 | 51 |
| Reflex absent | 5 | 5 | 10 |
| Total | 26 | 35 | 61 |
| All infants | | | |
| Reflex present | 33 | 44 | 77 |
| Reflex absent | 5 | 5 | 10 |
| Total | 38 | 49 | 87 |

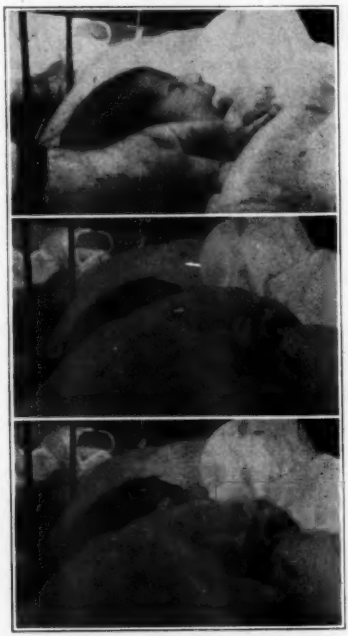
in response to an object. However, the dorsal extension frequently could be elicited even in such cases.

In general, the reaction begins with the extension of one finger, mostly either the fifth or the index, followed by the extension of the other fingers. When the reaction is strong, the thumb also is abducted and extended. While the extension reaction of the fingers is taking place, the wrist joint is often flexed a little and almost imperceptibly supinated. In some cases, however, simultaneously with the extension of the fingers, a strong dorsal flexion of the wrist was noted. The reaction seemed most consistent during the first days of life. Of the 17 infants investigated by me immediately after birth, the response to the cutaneous stimulation of the dorsal surface of the phalanges could be observed in 16. It appears to be a reaction which disappears in the

course of the first three months, definitely more rapidly than its opposite, the grasping reflex, which persists up to the fourth month.

Of the 36 infants to whom the stimulus was offered between the fourteenth and the twenty-first day of life, dorsal extension was observed in 29 but already could not be elicited in 7.

Like all other reflexes of the newborn infant, the production of this one was also somewhat dependent on subjective states and could be disturbed by sleep, screaming, discomfort, etc. In the newborn infants



Digital extension reflex.

that we have observed, however, this reflex could be elicited more reliably than any other, with the exception of the grasping reflex.

Table 3 shows vividly how far such reflexes as the Moro reflex, the sucking reflex and the cremasteric reflex fall behind in reliability when compared with the digital extension reflex.

Even the plantar reflex is not comparable in reliability to the digital extension reflex because of the unspecific forms it takes in the newborn. From the motion pictures I have observed that on plantar stimulation some reaction takes place if the stimulation is strong enough, but it may be flexion, it may be fanning or it may be extension.

The digital extension reflex, on the other hand, is quite univocal. It occurs especially in response to the tactile stimulation of the dorsal surface of the fingers, and it is always an extension and never a flexion. It is further evident from the figures that when compared to the grasping reflex it is slightly (though not significantly) more reliable.

There is no highly positive correlation between the presence of the digital extension reflex and the other reflexes which I have examined. An exception to this is the grasping reflex. Both the digital extension reflex and the grasping reflex are present with such regularity in the

TABLE 3.—*Reliability of Birth Reflexes*

| Reflex | Within First Week | | | Second Week or Later | | |
|---|---|---|---|---|---|---|
| | Present, % | Inconclusive, % | Absent, % | Present, % | Inconclusive, % | Absent, % |
| Moro | 52 | 23 | 25 | 72 | 16 | 12 |
| Sucking | 81 | 5 | 14 | 61 | 14 | 25 |
| Cremasteric | 60 | 10 | 30 | 40 | 8 | 52 |
| Grasping | 100 | .. | .. | 81 | 2 | 17 |
| Extension | 100 | .. | .. | 79 | 4 | 17 |

large majority of the cases that they can be said to correlate significantly.

It is rather striking that a reflex so important for survival as the sucking reflex in response to pressure on the cheek should be much less specific and much less reliable than these two reflexes of the hand, which, in the human being at least, do not appear to play as important a role in survival.

It should be mentioned that the 17 subjects examined by us immediately after birth were delivered without anesthesia or even sedatives.

## SUMMARY

A reflex dorsal extension of the digits elicited by cutaneous stimulation of the newborn infant is described.

# NEUROLOGIC CONDITIONS OCCURRING AS COMPLICATIONS OF PREGNANCY

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## INTRODUCTION

THE PURPOSE of this paper is to give a brief review of the various neurologic conditions which may occur during pregnancy and the puerperium. Any patient who has coma, convulsions or visual disturbances must be considered as having a neurologic disturbance. The attempt has been made to include not only those conditions that are direct results of pregnancy, which are few, but also those which may be

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aggravated or activated by pregnancy and those which may result from some procedure required during delivery. Those conditions have been excluded in which the association is merely that of coincidence, though exceptions have been made to this rule when it seemed wise to do so for purposes of differential diagnosis. I have tried to present something of the background from which the various neurologic syndromes arise, rather than to confine myself to the neurologic features alone. This is necessary in understanding fully the individual case and in making an intelligent and differential diagnosis. It is especially true when a patient is first seen and no records are available.

In the German medical literature of fifty years ago one finds a large number of articles dealing with neurologic conditions associated with pregnancy. In many instances these old observations are not based on adequate study as judged by modern standards and the conclusions are not supported by more recent articles. Such articles have been almost entirely discarded. Von Hösslin [1] presented a careful analysis of this material. I have, however, drawn heavily on more recent articles, including the excellent paper by Alpers and Palmer.[2] In addition to specific references, articles of general interest have frequently been cited.

## HYPERTENSIVE VASCULAR DISORDERS

### ECLAMPSIA

This terrible condition is, fortunately, one of the rarest of the toxemias of pregnancy, but it is estimated that it occurs in about 1 of 300 to 800 cases. There appears to be considerable variation in the incidence of the disease in different parts of the world. Primiparas are especially likely to have this complication. The onset of eclampsia may occur during the last trimester of pregnancy, during labor or immediately after delivery. Only rarely does it appear more than twenty-four hours post partum, but it has been known to occur as late as seven days after delivery.

As a rule, the convulsions, to which the term refers, are preceded by premonitory signs and symptoms, such as headache, hypertension of a moderate degree, albuminuria and edema, symptoms which are attributed to a preeclamptic toxemia. In many cases there are disturbances in vision—often sudden and severe amblyopia. The loss of vision may be considerable, but there is almost never complete blindness. Retinal edema and detachment, both easily seen with the ophthalmoscope, are

1. von Hösslin, R.: Die Schwangerschaftslähmungen der Mutter, Arch. f. Psychiat. **38**:730, 1904.

2. Alpers, B. J., and Palmer, H. D.: The Cerebral and Spinal Complications Occurring During Pregnancy and the Puerperium, J. Nerv. & Ment. Dis. **70**:465, 1929.

the principal causes of loss of vision. The common albuminuric retinitis is not seen in uncomplicated eclampsia. In other instances the convulsions develop unexpectedly, without preceding symptoms. The seizures are usually generalized and of great violence. They are apt to occur in sequence at brief intervals and are followed almost at once by coma. During this period there is usually abundant evidence of renal failure. There may be oliguria, or even suppression of urine. Albuminuria of a high grade is always present. Changes in the normal blood chemistry have been described but are not considered specific. The temperature is usually normal. The blood pressure is only moderately increased, from 140 to 200 mm. of mercury. A higher elevation of systolic pressure suggests hypertensive encephalopathy rather than eclampsia. After the convulsions cease, polyuria of a pronounced degree may occur.

The death rate is from 5 to 10 per cent. Death rarely occurs with the patient in status epilepticus. The convulsions cease, and the patient lapses into deepening coma. The urinary outflow is completely suppressed, and the temperature rises. In some cases the condition is complicated by the occurrence of a cerebrovascular accident. The course is then modified by the position and extent of the hemorrhage. The sudden appearance of a unilateral dilated pupil, stiff neck, hemiplegia or an abrupt rise in temperature usually means that the simple eclampsia has been complicated by intracranial bleeding. Often this hastens the fatal outcome.

If the patient survives, consciousness is usually regained promptly after the convulsions have ceased. Recovery is then rapid and complete. This is the expected outcome, which occurs in the overwhelming majority of cases. The outlook for recovery of vision is good. The retinas become reattached in most instances. The amblyopia due to the retinal edema disappears.

Kjelland [3] reported an instance of a compression fracture of the sixth thoracic vertebra which was the result of severe eclamptic convulsions. There were local pain, tenderness and limitation of movement of the back.

In a small number of cases, perhaps 5 per cent or more, there are evidences of destructive lesions in the brain. Intracranial hemorrhage may occur during the convulsions and is often rapidly fatal. The hemorrhage may vary from a few petechial spots to massive intracortical or intraventricular bleeding.

Parks and Pearson [4] recently emphasized the frequency of the complication of cerebral hemorrhage and reported 6 cases of their own

3. Kjelland: Eclampsia Puerperarum and Fractura Columnae, Acta obst. et gynec., Scandinav. **27**:297, 1947.

4. Parks, J., and Pearson, J. W.: Cerebral Complications Occurring in the Toxemias of Pregnancy, Am. J. Obst. & Gynec. **43**:774, 1943.

which were observed in a series of 41 cases of eclampsia. In 1933 King [5] found 44 cases of cerebral hemorrhage in a review of the literature. In such cases the diagnosis has been made by the presence of blood in the spinal fluid or at autopsy. In a number of cases in which recovery has occurred, hemiplegia, aphasia, hemianopsia or even cortical blindness has been described. In some cases with manifestations of this type softenings in the brain have been observed post mortem, and were evidently due to thromboses of cerebral arteries, or perhaps vascular spasm. In most of these cases, however, the patient has survived, and the precise nature of the lesion is uncertain. Israel and Alpers [6] reported a case of a fresh abscess of the brain which was unrecognized and which ultimately caused death.

In rare cases there has been evidence of diffuse cerebral damage of great severity. Thus, Löwenberg and Lossman [7] reported the case of a woman aged 20 who had eclampsia with convulsions lasting fourteen hours and was in coma sixty hours. She survived in a vegetative state for seven years, during which time she could not talk or understand and was capable of scarcely any motor activity except for respiration and swallowing. The findings in the brain at autopsy are given later.

In a small percentage of cases mental changes have been evident after eclampsia. The incidence has been estimated at 5 per cent, but no definite statement can be made with regard either to the incidence or to the eventual outcome, since this condition is often confused with the psychoses.

Collections of blood of surgical significance have been reported by Abbott.[8] He removed an intracerebral hematoma, with a successful result. In rare cases subdural hematomas have occurred which required drainage. When localizing neurologic signs appear after the onset of convulsions, a hemorrhage must be suspected. When the convulsions have been controlled, it may be wise to investigate such focal symptoms further by means of diagnostic trephination and ventriculography, although complications that can be relieved by neurosurgical procedures are rare.

In summary, the patient with eclampsia may (1) survive and make a complete recovery, (2) may die in coma after the convulsions stop

5. King, A. G.: Eclampsia Without Convulsions Terminating in Cerebral Apoplexy, J. A. M. A. **100**:15 (Jan. 7) 1933.

6. Israel, S. L., and Alpers, B. J.: Eclampsia, Cerebral Abscess and Hemorrhage, Am. J. Obst. & Gynec. **47**:551, 1944.

7. Löwenberg, K., and Lossman, R. T.: Atrophy of the Brain Following Puerperal Eclampsia, Am. J. Path. **19**:697, 1943.

8. Abbott, W. D.: The Surgical Treatment of Intracranial Hemorrhage Complicating Eclampsia and Encephalomalacia Limited to the Left Frontal Lobe, Am. J. Surg. **59**:113, 1943.

(cerebral edema?), (3) may die of cerebral hemorrhage, (4) may survive with hemiplegia or other signs of a focal cerebral lesion, (5) may survive with evidences of mental deterioration and (6) may survive with extensive and diffuse cerebral damage.

Autopsy shows extensive changes in the brain, which Löwenberg has summarized recently. Grossly, there is said to be congestion and edema, as well as small hemorrhages in the gray and the white matter. Microscopic examination shows that the severest changes occur at the junction of the cerebral cortex and the white matter but that there are also changes in the lenticular nuclei, the thalamus and the cerebellum. The process is said to include four components: (1) diffuse degeneration of the cerebral neurons; (2) small areas of necrosis in both the white and the gray matter; (3) small, and occasionally large, hemorrhages, and (4) small softenings due to hyaline degeneration of the vessels and thrombosis. These lesions are attributed to intoxication and to angiospasm or other functional disturbances of the circulation.

The brains of patients who have survived for long periods with severe neurologic symptoms may show extensive atrophy. Thus, Löwenberg stated that in his case the brain weighed only 579 Gm. and had probably lost over 60 per cent of its weight. There were extensive atrophy of the cortex and extreme demyelination. The lenticular nuclei, thalamus and cerebellum were severely damaged.

### HYPERTENSIVE VASCULAR DISEASE

The cause of this type of arterial hypertension is still obscure. At autopsy one finds arteriosclerosis and evidences of renal damage, but it is believed that these structural changes are secondary, and not the cause of the increased blood pressure.

This disease is one of the commonest complications of pregnancy. It must be differentiated from the preeclamptic and the eclamptic states. This differential diagnosis is not infrequently a difficult one, especially in the borderline cases.

In most cases the disease is probably present before pregnancy, but the patient and the physician may be unaware of this. In a few cases the hypertension may start during pregnancy, but this may well be coincidental. However, there appears to be considerable evidence that pregnancy may aggravate the disease and hasten its course.

If hypertensive vascular disease is present before conception, it may pursue one of several courses. In the majority of cases it is innocuous, and the pregnancy goes to term uncomplicated. Less commonly, but in a significant number of cases, preeclampsia develops. Occasionally the hypertension becomes malignant, and hypertensive encephalopathy develops. In rare instances acute malignant necrotizing endarteritis occurs. This form is almost universally fatal.

When the disease assumes a malignant character, cardiac, renal and cerebral changes are apt to appear. Only the associated neurologic symptoms will be mentioned and discussed.

Headache is a prominent feature and may be the only symptom. In some instances the headache parallels the level of the blood pressure. Visual disturbances are common. Papilledema is not unusual and may be associated with gross reduction of vision, though rarely with blindness. Retinal hemorrhages are often seen, and there may be exudates as well. Edema of the retina is described, and in rare instances detachment. Transient loss of vision of a few seconds' duration is well known in such cases, and, since nothing to explain this may be found on ophthalmoscopic examination, it has been assumed that spasm of the retinal arteries is to blame. Transient cerebral palsies are typical of this condition. Hemiplegia, monoplegia, hemianopsia or aphasia may appear with or without convulsions and rapidly disappear without residua. As a rule, these complications occur only when the blood pressure is very high. Unfortunately, persistent cerebral syndromes are also observed. These are due to thrombosis of cerebral arteries or to cerebral hemorrhage. Hemorrhage is, of course, a serious and often fatal complication, for the blood vessels may rupture into the subarachnoid spaces and also into the ventricular system, causing extensive laceration of the brain and increased intracranial pressure. There is profound shock in such episodes. In some cases the hemorrhage may become encapsulated and behave like a tumor, so that in a few instances the blood may be evacuated through a large needle.

In some instances there is a sudden and abrupt elevation of the blood pressure above the previous level, with the production of acute cerebral symptoms. This condition is termed hypertensive encephalopathy. There are violent headaches, vomiting, reduction of vision, mental confusion and convulsions. The convulsions are often followed by transient focal palsies of cerebral origin. There is a sudden appearance of retinal hemorrhages and occasionally of subhyaloid hemorrhages. The retinal arteries show pronounced spasm and may be reduced to threads. Papilledema and increased spinal fluid pressure indicate an increase of intracranial pressure. Renal function is not always significantly reduced. The symptoms parallel the blood pressure. The patient may die in a few days; but if death does not occur the symptoms are likely to recede in a short time, for this is a condition of brief duration. If death occurs in the acute stage, postmortem examination may reveal marked edema of the brain, associated with flattening of the convolutions and reduction of the ventricular volume. Cerebellar pressure cones are usually present.

Petechial hemorrhages are found scattered throughout the brain. Occasionally gross hemorrhages are present, the effects of which may have been masked by the convulsions and coma. Subarachnoid bleeding is frequent.

This complication may be very difficult to distinguish from eclampsia. A history of preceding hypertension is most valuable. Information concerning preceding transient cerebral palsies, blindness and severe headache is most valuable. The blood pressure is nearly always over 200 mm. of mercury, often in the region of 250 mm. in cases of hypertensive encephalopathy. Eclamptic patients usually have a less pronounced hypertension, in the range of from 140 to 200 mm. of mercury. The ophthalmoscopic picture is not specific for either condition, but in eclampsia the retinal edema is often much more pronounced than in hypertensive encephalopathy.

In many cases the diagnosis is not fully resolved even at the autopsy table, since in cases of eclampsia there may not be specific lesions. After delivery the hypertension associated with eclampsia usually falls to normal and all symptoms disappear. In hypertensive vascular disease the blood pressure remains elevated after delivery, but it may drop to a lower level. It should be mentioned, however, that I have seen several women for whom sympathectomy was recommended for relief of hypertensive vascular disease who gave a history of eclampsia several years before. Much remains to be done in the clarification of these two conditions.

## CONDITIONS DUE TO VASCULAR DISORDERS

### POSTPARTUM THROMBOSIS (NONSEPTIC) OF THE CORTICAL VEINS AND DURAL SINUSES

In papers dealing with hemiplegia following delivery one finds an occasional instance in which the lesion was shown to be due to thrombosis of the venous channels[9]. As a rule, the pathologic changes are described so briefly that it is impossible to discover the true nature of the process, and septic and nonseptic thromboses are not sharply distinguished. Recently, however, papers by Martin and Sheehan[10] and Symonds[11] have clarified the situation. They have made it clear that primary thromboses of the cerebral veins and dural sinuses may occur after delivery without apparent cause and that a well defined clinical picture results.

The onset is between the first and twentieth day after delivery, which is as a rule uncomplicated. The illness is initiated by hemiplegia

9. Collier, W.: Thrombosis of the Cerebral Vein, Brit. M. J. **1**:521, 1891. Hunt, J. R.: Thrombosis of the Cerebral Sinuses and Veins as Complications of the Puerperium, Bull. Lying-In Hosp., New York, **11**:73, 1917.

10. (*a*) Martin, J. P.: Thrombosis in the Superior Longitudinal Sinus Following Childbirth, Brit. M. J. **2**:537, 1941. (*b*) Martin, J. P., and Sheehan, H. L.: Primary Thrombosis of the Cerebral Veins Following Childbirth, ibid. **1**:349, 1941.

11. Symonds, C. P.: Cerebral Thrombophlebitis, Brit. M. J. **2**:348, 1940.

or by convulsions, which are usually focal but may be generalized. The seizures may cease in a few hours or may continue for several days. If they recur after an interval, this may be taken to indicate an extension of the thrombus. In some cases the patient regains consciouness at once after a seizure, but in others the stupor persists and passes into coma. If the coma is of long duration, the outlook is considered unfavorable. Paralysis is observed to follow the convulsion in a large percentage of cases. This may involve the arm, the arm and face or the arm, face and leg. In the same way, cortical anesthesia with or without hemiplegia and aphasias of various types may occur. Headache and vomiting may appear, and later the optic nerve heads often show papilledema. This is taken to indicate that the thrombus has extended so as to occlude the superior longitundinal sinus and is causing congestion and edema of the brain. The spinal fluid may be clear or may contain a little blood. Usually the pressure is elevated. As a rule, there is only a moderate and brief elevation of temperature. Martin[10a] mentioned an instance in which a transverse lesion of the spinal cord developed, in addition to the cerebral symptoms.

If the process is very extensive, death may result from the intracraniel process or from embolism to the lungs. As a rule, however, the patient survives, and there is a tendency for the paralysis to recede, or even to disappear.

Postmortem examination and surgical exploration have revealed thrombosis of the cortical veins which drain into the superior longitudinal sinus, more especially the rolandic vein. The thrombus may extend into the superior longitudinal sinus and cause extensive venous obstruction. The damage to the brain is determined by the extent of the thrombus and the anatomy of the venous channels, which are, of course, subject to numerous anatomic variations. Hemorrhagic infarction results in those areas in which the circulation is interrupted. Martin and Sheehan[10b] described hemorrhagic softenings, 3 to 5 cm. in diameter, situated in the rolandic region and in the frontal and parietal lobes. In cases in which autopsy is done years later, one finds only pigmented scars, for the veins have become recanalized.

In typical cases the diagnosis would seem to be easy. The onset of convulsions shortly after delivery, followed by hemiplegia and then by signs of increased intracranial pressure, would seem to be characteristic, especially if there is no hypertension, infection or evidence of toxemia. We have observed the onset of extensive paralyses without any evidence of shock, which would be expected if the lesion were due to arterial thrombosis. There is also reason to think that the paralyses tend to recede somewhat more satisfactorily than is usual with arterial lesions.

The cause of this condition is not clear. It is not as a rule associated with excessive loss of blood, with toxemia or with clinical or postmortem

evidence of infection. In most instances there is no evidence of pelvic phlebitis. Possibly the slight clotting tendency which the blood exhibits during the puerperium may play a role. Some authors have suggested that a few bacteria may be carried by the blood stream to the cerebral veins and there set up a thrombosis, which, despite its bacterial origin, does not lead to an abscess. Martin suggested that bits of blood clot are carried from the pelvic veins by way of the paravertebral venous plexus to the cranium. He referred to the work of Batson[12], who claimed that carcinoma may extend by this route and so avoid the capillaries of the lungs.

One of the cases from the Johns Hopkins Hospital is presented by way of illustration.

***Sudden development of right hemiplegia and hemianopsia and aphasia on the day after delivery. Headache, vomiting and diplopia, appearance of papilledema later. Absence of abnormalities in the ventriculogram. Ventricular fluid xanthochromic. Incomplete recovery with mental changes, convulsions and residua of the focal signs.***

P. K., a previously healthy woman aged 20, was delivered of a healthy infant on Nov. 26, 1943. Pregnancy had been uneventful, and delivery was spontaneous and easy. Approximately twenty-four hours later, there suddenly developed complete right hemiplegia and loss of the power of speech. This occurred within a period of a few hours. There was never any loss of consciousness, and no convulsive phenomena were noted. There was only a brief and moderate elevation of temperature. Examination on the third day after the onset, i. e., November 30, revealed hemiplegia, hemianesthesia and hemianopsia on the right side. There was an incomplete global aphasia, but except for the disorder of speech the patient's mental reactions seemed clear. The optic nerve heads were normal, and there was no particular complaint of headache. There was no evidence of postpartum infection.

On December 6, violent headaches developed, with vomiting and double vision. These episodes continued, and on December 10 there were outspoken bilateral papilledema and paralysis of the left sixth nerve. There was moderate bradycardia. At this time the hemiplegia had receded somewhat, and it was then evident that there was ataxia on the right side, due, no doubt, to the loss of proprioception. The hemianopsia had disappeared. The aphasia was still present, and there seemed to be apraxia on the left, for she could not feed herself with her left hand, despite the absence of any simple motor or sensory disorder on that side.

The papilledema gradually increased in severity, and on December 20 she was admitted to the service of Dr. Walter Dandy. The optic disks were then elevated 5 or 6 D., and there were hemorrhages in both retinas. The neurologic findings were unchanged otherwise. The blood pressure was 110 systolic and 65 diastolic. The temperature was normal; the pulse rate was 62. The Wassermann reaction of the blood was negative. The cerebral ventricles were punctured, and air was injected. Yellow fluid was secured, under increased pressure. Roentgenograms revealed no abnormalities of the ventricular system. The patient was discharged on December 30, without treatment. The papilledema was beginning to recede at that time.

Subsequent improvement was slow. The headaches and the signs of increased intracranial pressure disappeared. The hemiplegia and hemianesthesia also receded,

12. Batson, O. V.: Function of the Vertebral Veins and Their Role in the Spread of Metastases, Ann. Surg. **112**:138, 1940.

though slight residual weakness and increase of tendon reflexes, especially in the right leg, persisted. Speech improved strikingly, though it never attained its proper fluency. There were mild mental changes, for the patient was forgetful and irritable and was not able to manage her household accounts. She found reading very difficult. In 1944 she began to have seizures. These as a rule were confined to the right side and were usually purely sensory. Sometimes she would have motor fits on the right side, and twice she had generalized convulsions with loss of consciousness. When she was last seen, on May 20, 1947, her status was unchanged. She was having an average of one seizure in two months, despite sedative treatment.

It was assumed that the patient had nonseptic thrombosis involving the cortical veins draining the lateral aspect of the left hemisphere and causing softening, and that later the process extended so as to produce a more extensive interference with venous drainage and increased intracranial pressure.

### UNEXPLAINED ARTERIAL OCCLUSION OR HEMORRHAGE INVOLVING THE BRAIN OR THE SPINAL CORD

In other sections of this paper a number of conditions have been mentioned which may give rise to vascular lesions involving the nervous system. At this point, it may be pointed out that numerous cases have been recorded of cerebral, or even spinal, vascular accidents developing during pregnancy or during the puerperium for which no cause could be found. Numerous cases of intracranial hemorrhage have been described, as well as cases of softening due to arterial thrombosis or embolism. It must be admitted that in most instances the clinical examinations have been incomplete and the postmortem studies inadequate. One gains the impression that unexplained vascular lesions in the brain during the puerperium are usually the result of venous thrombosis, as described elsewhere.

Meltzer [13] mentioned the case of a woman aged 32 in whom right hemiplegia and aphasia developed ten days after delivery and thrombosis of the left middle cerebral artery was observed at autopsy. Thompson [14] described the case of a woman aged 33 who on the seventh day after a postpartum hemorrhage exhibited right hemiplegia and thrombosis of the central retinal artery in the left eye. Von Hösslin [1] and Alpers and Palmer [2] mentioned a number of cases of similar type, in most of which the examinations were incomplete. I have observed several instances of unexplained hemiplegia in young women, all of whom survived.

A number of spinal syndromes which were associated with pregnancy have also been described. Alpers and Palmer [2] collected a number of such cases. A notable case is that of Bruce,[15] in which during the fifth month of pregnancy a hemorrhage developed in the dilated central

13. Meltzer, T.: Neurologic Complications in the Mother Following Pregnancy, J. Nerv. & Ment. Dis. **96**:641, 1942.

14. Thompson, A. M. W.: Postpartum Retinal Arterial Obstruction Associated with Hemiplegia, Brit. M. J. **1**:387, 1940.

15. Bruce, A.: Hemorrhage into the Spinal Cord During Pregnancy, Scottish M. & S. J. **11**:107, 1902.

canal, a condition which is usually termed hydromyelia. I have observed a case in which a lesion suddenly developed in the thoracic portion of the spinal cord during delivery. At operation it was clear that a small hemorrhage had formed on the anterior lateral aspect of the spinal cord, but only operative observations were possible and the true nature of the lesion remained obscure.

### AIR EMBOLISM DURING DELIVERY OR THE PUERPERIUM

Occasional cases have been reported in which sudden death followed intrauterine manipulations, especially in cases of placenta previa or rupture of the uterus. Such fatalities are attributed to air embolism. The same condition may result from the injection of air into the pregnant uterus in an effort to produce abortion. A number of such cases have been reported, including 6 by Strassmann,[16] all of which represented attempts at criminal abortion. It is believed that air enters the uterine sinuses and is thence carried to the heart, the lungs and the systemic circulation. About a dozen cases have been described in which the same events occurred during the puerperium. These will now be discussed.

Legallois[17] observed evidences of air embolism in rabbits during the postpartum period and suggested that the same phenomenon might occur in human subjects. It was not until the reports of Cormack,[17] in 1850, and May,[17] in 1851, that human fatalities were recorded. Since then occasional cases of this condition have appeared in the medical literature. Garcin and associates[17] attributed 2 cases of hemiplegia to this cause, although the patients survived.

A typical instance of this condition is the case published by Redfield and Bodine.[18] Their patient, a woman aged 33, a bipara, had convulsions on the eleventh day post partum, immediately after having completed some knee-chest exercises. She died within twelve minutes. At autopsy the uterus was found to be filled with blood clots. Many uterine veins were open and gaping, and several were filled with frothy blood. The right side of the heart contained air.

A typical nonfatal case is that of Rangell.[19] A primipara, aged 24, had just completed her first set of knee-chest exercises on the seventh postpartum day, when she gave a deep groan, became rigid and had a convulsion. She remained comatose for two days. During this time she had several convulsions, starting in the right leg. She then recovered consciousness but was confused and excited. It was necessary to transfer her to a psychiatric hospital, where she had visual hallucinations and feelings as though she were floating. After four days the symptoms began to disappear, and she made a rapid recovery, the only residuum being amnesia for the events of her illness.

16. Strassmann, G.: Ueber Todesfälle durch Luftembolie bei kriminellem Abortus, Monatsschr, f. Geburtsh. u. Gynäk. **81**:269, 1929.

17. Cited by Rangell.[19]

18. Redfield, R. L., and Bodine, H. R.: Air Embolism Following the Knee-Chest Position, J. A. M. A. **113**:671 (Aug. 19) 1939.

19. Rangell, L.: Cerebral Air Embolism, J. Nerv. & Ment. Dis. **96**:542, 1942.

It is not easy to understand how the air may be introduced into the circulation, but in certain circumstances it appears to be possible. One apparently must assume that there are retained membranes and clots which may be dislodged and leave the venous sinuses open. The performance of the knee-chest exercises seems to be an essential factor, if one may judge by the case histories which have been published. Two mechanisms may be suggested. 1. While the patient is in the knee-chest position, the falling forward of the abdominal viscera may create a negative pressure in the venous system of the pelvis, resulting in aspiration of air into the patent uterine sinuses. 2. In this position, the vagina and uterus may become filled with air, since the labia are open; and on resumption of the prone position, when the labia are closed by the thighs, the pressure of the body weight on the abdomen results in compression of the trapped air and its entrance into the uterine sinuses. It is not known how much air must be introduced to produce symptoms. No doubt, 30 to 50 cc. or more is required.

It is not difficult to explain the symptoms once the air has got into the circulation. They are well known and have been produced experimentally many times. When large amounts of air enter the right side of the heart rapidly, an air block seems to be produced, since the heart valves are not competent for air. Cerebral anoxia, therefore, results. It is known, however, that air may get into the arterial circulation even in the absence of a patent foramen ovale and ductus arteriosus. Perhaps minute air emboli pass through the pulmonary capillaries and subsequently unite to form larger bubbles, which may occlude the capillaries of the brain, retinas and other organs.

My colleagues and I have observed coma and convulsions followed by hemiplegia, double hemiplegia, hemianopsia and blindness in patients with air embolism. These complications did not occur in the puerperium, but no doubt the symptoms are essentially the same no matter how the air is introduced. With few exceptions, these symptoms have disappeared if the patients survived, but residua are known to have persisted.

There is no accepted treatment once the condition has developed. Since air embolism seems to occur after the use of vaginal insufflations or the performance of knee-chest exercises shortly after delivery, it might be wise to abandon both these procedures. Oxygen should be administered, and venesection may be helpful in relieving the load on the right side of the heart. Puncture and aspiration of the right ventricle have been used with success in experimental animals.

### EMBOLISM DUE TO AMNIOTIC FLUID CONTENTS

Steiner and Lushbaugh [20] claimed that amniotic fluid may gain entrance to the circulation during delivery and, since it contains various

20. Steiner, P. E., and Lushbaugh, C. C.: Maternal Pulmonary Embolism by Amniotic Fluid, J. A. M. A. **117**:1245 (Oct. 11) 1941.

particles of solid matter, give rise to pulmonary embolism and death. They based this belief on the postmortem examinations of 8 women who died suddenly during delivery. They found that many of the small arteries, arterioles and capillaries of the lungs were occluded by emboli which were composed of meconium, leukocytes, vernix caseosa, lanugo hair and squamous material. It was apparent that death was due to anoxemia resulting from obstruction of the pulmonary circulation. These authors were able to reproduce the clinical and anatomic picture by intravenous injection of amniotic fluid in experimental animals.

The clinical picture is described as follows: During labor, or immediately afterward, the patient suddenly exhibits dyspnea, cyanosis and confusion, which may be followed by convulsions and by coma. Vomiting is common. The blood pressure falls alarmingly, and the pulse becomes rapid and feeble. Rales are heard in the chest. Death may occur in a matter of minutes or may be postponed for a few hours.

The elucidation of these symptoms seems to require several assumptions. One must assume that the rupture of the membranes occurs in such a manner that the amniotic fluid comes into direct contact with the uterine walls. Moreover, the placenta must be at least partially detached, so that some of the uterine sinuses are exposed. If the cervix is now obstructed by the fetal head and the uterus contracts forcefully, it is evident that the amniotic fluid may be forced into the venous system, and ultimately to the lungs. Since it contains particulate matter, embolism may result.

The neurologic symptoms are apparently a result of cerebral anoxia, since there is no proof that such emboli can pass through the pulmonary capillaries except in cases in which a patent foramen ovale or ductus arteriosus exists.

The incidence of this remarkable occurrence is not known. Lushbaugh and Steiner [21] stated the opinion that it may cause death once in 8,000 deliveries. They found a less extensive embolism in the lungs of women who had died of other causes and suggested that a minor degree of this condition may occur frequently without giving rise to symptoms.

### RUPTURE OF DISSECTING ANEURYSM DURING PREGNANCY

In a recent review of the literature, Schnitker and Bayer [22] drew attention to the fact that rupture of a dissecting aneurysm is not infrequent in persons under the age of 40, and is especially likely to occur

21. Lushbaugh, C. C., and Steiner, P. E.: Additional Observations on Maternal Pulmonary Embolism by Amniotic Fluid, Am. J. Obst. & Gynec. **43**:833, 1942.

22. Schnitker, M. A., and Bayer, C. A.: Dissecting Aneurysm of the Aorta in Young Individuals Particularly in Association with Pregnancy, Ann. Int. Med. **20**:486, 1944.

during pregnancy. They were able to collect statistics on 580 cases in all age groups, and 141 (24.3 per cent) of these were of patients less than 40 years of age. The youngest patient was a child of 4½ years. Of the patients under the age of 40 years, 92 were males and 49 females. Of the women, 24 were pregnant at the time of rupture.

In the majority, rupture occurred during the last trimester of pregnancy. It developed before the beginning of labor in a total of 20 cases. Schnitker and Bayer suggested that disturbances of lipid metabolism in pregnancy may initiate or aggravate the process. The strain and exertion of labor appear to play no significant role.

The clinical picture is typical. There is, as a rule, a sudden terrific pain in the chest, with a crushing sensation beneath the sternum. The pain may radiate into the arms, neck, head, abdomen or legs. The patient may describe a sensation of something tearing. Almost immediately there are dyspnea, cyanosis and extreme weakness. Death may occur almost at once or after as long as two weeks. The fatal outcome may be due to bleeding into the pericardium, with cardiac tamponade, or may result from congestive heart failure or uremia if the dissection has included both renal arteries.

Partial or complete paraplegia with flaccidity, urinary retention and sensory loss may occur if the blood supply to the spinal cord is seriously embarrassed, as a result of obstruction of the intercostal and lumbar arteries. If the carotid or innominate arteries are involved, there may be ischemic necrosis of the brain. Confusion, stupor, convulsions, hemiplegia or aphasia may be present, depending on the degree of circulatory obstruction. Hoarseness and dysphagia may occur, possibly owing to pressure on the recurrent laryngeal nerve and the esophagus. If the carotid artery is dissected high enough that the ophthalmic artery is occluded, blindness may result. In some cases the extremities are cold, numb and weak, and this condition has been attributed to reduction of the circulation of the limbs and ischemia of the nerve trunks.

The cause of this condition is not entirely clear. Hypoplasia or coarctation of the aorta was present in 31.9 per cent of the cases. Trauma, developmental defects, hypertension and arteriosclerosis were noted in some cases.

The pathologic process is said to be a cystic degeneration of the media, principally in the ascending arch. Erdheim (cited by Schnitker and Bayer) called the lesion medionecrosis cystica. The site of the tear is in the ascending aorta in 70 per cent of cases. Schnitker and Bayer suggested that degeneration of the media causes rupture of small nutrient vessels, with the formation of intramural hematoma. This, in turn, produces pressure necrosis in the overlying intima. The intima gives way, allowing an ingress of aortic blood under high pressure, causing the extensive dissection which one finds at autopsy.

The differential diagnosis includes myocardial infarction, acute perforation of an abdominal viscus and rupture of an intervertebral disk in the cervical region. Kinney and associates [23] reported a case in which herniation of a cervical disk was simulated. The physical signs and roentgenograms of the chest usually enable one to arrive at a proper diagnosis.

Treatment includes use of large doses of morphine and administration of oxygen. The outlook, of course, is exceedingly grave.

### UREMIA AND OTHER CONDITIONS ASSOCIATED WITH NEPHRITIS

Acute nephritis is an extremely rare complication of pregnancy. Chronic nephritis is also rarely encountered among pregnant women, but Miller,[24] in an able review of the subject, reported 3 cases per thousand deliveries, although he admitted that this figure was high, owing to selective admissions to his hospital. Since women with nephritis rarely become gravid, the common neurologic symptoms of this condition are most uncommon in an obstetric service. Only a few women with this disease will go on to frank renal failure during pregnancy.

I am concerned not with nephritis per se, but with the various effects of renal insufficiency on the nervous system. The diverse neurologic symptoms seen in association with chronic nephritis are produced either by the changes in body chemistry or by the associated hypertension or by a combination of the two.

Severe headaches, lassitude and dizziness may be the presenting symptoms of a uremic state, although restlessness and excitement may occur first. Visual symptoms, such as blurring, photophobia and transient amblyopia, appear. As the degree of failure proceeds, nausea and vomiting may occur.

Edema is one of the cardinal symptoms. It may vary from a slight puffiness about the eyelids to profound anasarca. Evidences of increased intracranial pressure may be observed, such as papilledema, bradycardia and an increase in spinal fluid pressure. In the terminal stages convulsions are common and may be followed by coma, which, however, may supervene without preceding convulsions.

The hypertension that is associated with nephritis may be the cause of another train of symptoms. A pounding, throbbing headache that persists for days may be the predominant complaint. There are transient cerebral palsies, monoplegias, hemiplegias and aphasias, due to vasospasm or occlusion of small cerebral vessels. A sudden and prominent hemiplegia, hemianopsia or aphasia is the result of the

23. Kinney, T. D.; Sylvester, R. E., and Levine, S. A.: Coarctation and Acute Dissection of the Aorta Associated with Pregnancy, Am. J. M. Sc. **210**:725, 1945.

24. Miller, D.: Observations on Eclamptic Toxaemia and on Essential Hypertension and Chronic Nephritis in Pregnancy, Edinburgh M. J. **49**:209, 1942.

occlusion of a major cerebral artery. This may or may not be accompanied with a period of unconsciousness. Signs of subarachnoid or intracortical hemorrhage mean that a vessel has ruptured.

Uremia without hypertension is sometimes seen. Dizziness and clouding of consciousness are the most obvious symptoms. The patient may sink into coma and die as though of barbiturate poisoning. As a rule there are no convulsions, but the picture may be complicated by tetany. There are no transient cerebral palsies or signs of increased intracranial pressure. The retinas may show no changes except in the blood vessels.

It is well known that tetany may appear as the result of renal damage. This may be manifest by convulsions, by muscular twitchings or carpopedal spasms or by the signs of latent tetany. Apparently, the tetany is due to the retention of phosphates and the relative reduction of calcium ions.

Since many of the signs and symptoms here noted are similar to those associated with the toxemias of pregnancy, it is necessary to be sure whether one is dealing with nephritis or with a toxemia. The symptoms due to nephritis are nearly always seen much earlier in the course of pregnancy than those of the toxemias. A careful history will often elicit the history of a past attack of nephritis. Physicial examination will frequently disclose structural changes in the cardiovascular system, such as sclerotic radial and retinal arteries and cardiac enlargement. The hypertension is higher than that encountered in the toxemias, and renal damage is more profound. Again, it should be emphasized that both acute and chronic nephritis are rarely encountered during pregnancy.[24]

The ophthalmoscopic picture may be extremely helpful. Hard, brilliant exudates scattered through the fundi with a macular star point to chronic nephritis. Flame-shaped retinal hemorrhages are common. The arteries are often reduced in caliber and show pronounced thickening of the walls, producing a silver and copper wire appearance. The optic disks may be blurred or may show an outspoken papilledema.

A disturbance of the potassium metabolism has recently been reported in connection with renal failure.[25] So far as I know, this has not been described as a complication of pregnancy, but possibly it has been overlooked. A syndrome resembling periodic familial paralysis attributed to low serum potassium has been distinguished. There is a rapidly developing flaccid paralysis of the skeletal muscles with loss of reflexes, but no disturbance of sensibility or consciousness. Prompt relief of symptoms follows the administration of potassium salts.

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25. Brown, M. R.; Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, J. A. M. A. **124**:545 (Feb. 26) 1944.

A paradoxic claim has also been made that retention of potassium may produce rapidly ascending flaccid paralysis with loss of tendon reflexes.[26] This is associated with a very high level of serum potassium. The condition may be relieved by the administration of sodium chloride. The two types of paralysis are distinguished not only by the level of the potassium in the blood but by the changes in the electrocardiogram. In the variety due to potassium deficiency, the T wave is depressed, while in the type due to a potassium excess the T wave is elevated.

## METABOLIC DISORDERS

### DIABETES WITH DIABETIC COMA AND HYPOGLYCEMIC COMA

Before the introduction of insulin, women with diabetes of moderate or severe degree were unlikely to conceive, for this condition is apt to be associated with sterility. Occasionally, however, a young woman with diabetes would become pregnant, and in that case there was usually a pronounced exacerbation of the disease, which frequently led to diabetic coma and death, since it was at that time impossible to regulate the disease satisfactorily. A paper by J. Whitridge Williams,[27] published in 1909, revealed what a threat pregnancy held for the diabetic woman in those days, for he estimated the mortality at 45 per cent.

Since insulin has become available, and since laboratory facilities for proper study of metabolism have been developed throughout the country, the situation has undergone a profound change. Sundelin reported that the incidence of pregnancy in females of suitable age had risen from 2 to 15 per cent. It is, of course, now possible to maintain proper regulation of this disease throughout pregnancy in most instances. The maternal mortality is now estimated to be between 1 and 3 per cent, and diabetic coma accounts for few of the fatalities. Though difficult problems in management present themselves from time to time, especially in connection with acute infections, it may be said that at present the development of diabetic coma during pregnancy is almost invariably the result of inadequate care, owing to neglect on the part of the physician or failure of the patient to follow directions.[28] Patients who survive diabetic coma exhibit no evidences of lasting damage to the central nervous system so far as I have been able to ascertain.

Certain new problems, however, have presented themselves. Hypoglycemic coma has become a well known reaction in patients treated with insulin. As a rule, this is a result of an overdose of insulin or of an inadequate food intake, but there is sometimes a spontaneous reduc-

26. Finch, C. A.; Sawyer, C. G., and Flynn, J. N.: The Clinical Syndrome of Potassium Intoxication, Am. J. M. Sc. **1**:337, 1946.

27. Williams, J. W.: The Clinical Significance of Glycosuria in Pregnant Women, Am. J. M. Sc. **137**:1, 1909.

28. Joslin, E. P.: Diabetes Mellitus, New England M. J. **232**:219, 1945.

tion of insulin requirements in the last few weeks of pregnancy and in the puerperium which leads to the development of this condition unless the physician is on the alert. In some women the sugar metabolism is subject to such wide fluctuations that hypoglycemic reactions are avoided only with the greatest difficulty. It must be pointed out that hypoglycemia may inflict serious damage on the brain, which may lead to the so-called irreversible coma, and that some patients who survive display evidences of organic changes in the nervous system manifest chiefly by mental deterioration. A number of studies have been made on the anatomic process, which is characterized by widespread degeneration and necrosis of the cortical nerve cells and the cells of the lenticular nuclei, with less striking lesions in the cerebellum.[29]

Diabetic polyneuritis and diabetic pseudotabes are sometimes seen in pregnancy. Rundles [30] pointed out that about one fourth of the neuropathies due to diabetes occur in persons below the age of 40. The same statement can be made regarding the palsies of individual cranial and spinal nerves. In the younger age group, the neuritis clears more rapidly and completely than in the aged. The autonomic nervous system is often severely affected and produces such diverse symptoms as neuropathic joints, grossly disturbed gastrointestinal and genitourinary function and abnormal orthostatic regulation of the blood pressure.[30] The appearance of these neuropathies is almost always due to grossly neglected or mismanaged diabetic treatment. In order to avoid serious and permanent injury to the nervous system, it is essential that the diabetes be expertly treated.

### HEPATIC DAMAGE DURING PREGNANCY

Acute yellow atrophy is a rare condition, and is one of the most fatal of the toxemias. Its incidence is not entirely clear, since acute yellow atrophy occurs in other states besides pregnancy. Baens and Espinola [31] described 6 cases which occurred in a series of 53,129 pregnancies, an incidence of 1 in 8,855. Sheehan,[32] in Scotland, found 6 cases in a series of 400 consecutive postmortem examinations made on women who had died as a result of pregnancy. Since the etiology is unknown and the pathologic findings are not unequivocable, it is difficult to get accurate statistics. Recently it has been suggested that the condition may be merely acute infectious hepatitis occurring in pregnancy. It

29. Lawrence, R. D.; Meyer, A., and Nevin, S.: The Pathological Changes in the Brain in Fatal Hypoglycemia, Quart. J. Med. **11**:180, 1942.

30. Rundles, R. W.: Diabetic Neuropathy, Medicine **24**:110, 1945.

31. Baens, A., and Espinola, N.: Acute Yellow Atrophy of the Liver in Pregnancy, J. Philippine Islands M. A. **17**:679, 1937.

32. Sheehan, H. L.: The Pathology of Acute Yellow Atrophy and Delayed Chloroform Poisoning, J. Obst. & Gynaec. Brit. Emp. **47**:49, 1940.

would appear, however, that the pregnant state plays some role. Stander and Cadden [33] found that 60 of the reported cases occurred during pregnancy.

The onset is usually between the thirty-sixth and the fortieth week but may be delayed until the puerperium. It is frequently abrupt but may be more gradual. Headache, vomiting, diarrhea, abdominal pains and confusion are among the early symptoms. There may be delirium and excitement for a time, but soon stupor develops, which is followed by coma. Convulsions are common. Death ensues within a few days in almost all cases. Jaundice is usually present and may be either mild or intense. The urine is scanty and contains albumin, and often blood. The pulse and respirations are rapid. The blood pressure is normal until renal failure occurs near the end. Stander and Cadden stated that the blood serum shows an increase of amino acids and of uric acid, whereas the blood sugar and urea are decreased. The icteric index of the blood is increased, but the van den Bergh reaction is biphasic, a situation which is not very helpful in establishing a diagnosis.

The diagnosis is often difficult, probably owing in part to its rarity and often to the variable clinical course. In Europe, however, where there would appear to be a greater number of cases, diagnosis is said to be easy.[32]

Autopsy findings often do not settle a disputed case. In a typical case, the liver is small, shrunken and yellow and its lobular pattern is lost. Microscopic examination discloses fatty changes which involve the entire lobule except for a narrow zone of cells lying around the periphery. The affected cells are filled with minute, fatty vacuoles. In more advanced cases, some pathologists state, there is extensive necrosis, which involves all but the most peripheral cells. Sheehan disputed this, and stated that necrosis is periportal and minimal. If the patient survives more than two weeks, no necrosis is found. The kidneys show changes indicative of acute nephritis, the tubules being affected more than the glomeruli.

Severe damage to the liver may also be caused by a variety of drugs used in connection with the pregnancy. In addition to chloroform, arsphenamine, phosphorus, carbon tetrachloride and cinchophen derivatives may be mentioned. DeLee [34] claimed that chloral and gas anesthetics may produce similar syndromes.

While the use of chloroform is not widespread in this country, it is not infrequently used abroad. It had been used in 14 cases in a series of 400 autopsies on women dying in pregnancy reported by Sheehan.[32]

33. Stander, H. J., and Cadden, J. F.: Acute Yellow Atrophy of the Liver in Pregnancy, Am. J. Obst. & Gynec. **28**:61, 1934.

34. DeLee, J. B.: Principles and Practice of Obstetrics, ed. 8, Philadelphia, W. B. Saunders Company, 1943, p. 376.

It appears that pregnancy makes the woman more susceptible to hepatic damage from this drug. The amount of chloroform administered seems to be of little importance, and it has been thought that inadequate food, prolonged labor, dehydration and acidosis predispose to this reaction. The clinical syndrome is almost identical with that of acute yellow atrophy, already mentioned. The symptoms usually develop on the second or the third day after delivery. Death may occur within a few hours, or the patient may survive. The outlook is much better than in cases of hepatic damage of unknown origin. Postmortem studies disclose that the liver is not shrunken, but is of almost normal size. Microscopic sections show anything from a few scattered necrotic cells to pronounced midzonal necrosis.

The diagnosis of hepatic damage due to a chemical poison is usually not difficult if a proper history can be obtained. Patients not seen until coma or convulsions have appeared present a difficult problem. The presence of jaundice should suggest a toxin, and the patient's relatives and aquaintances should be carefully questioned concerning the possible administration of chloroform or other chemicals noted in the previous paragraph.

### TETANY DURING PREGNANCY AND LACTATION

Although it has long been known that tetany may occur during pregnancy, it is a most unusual complication. Its incidence in this country is very low, but it is probably higher in some European and Asiatic countries, in which diets are frequently deficient.

It seems to be clearly established that most forms of tetany are due to low serum calcium, or at least to a low concentration of calcium ions in the serum. Apparently, parathyroid deficiency is the commonest factor, which occurs spontaneously without apparent cause except in some instances, when it is the result of injury to the parathyroid glands during operation on the thyroid. A diet deficient in calcium and in vitamin D is another cause, and diarrhea and persistent vomiting may be mentioned as other possible etiologic factors. There is no doubt that pregnancy will often produce active tetany in women who were free from symptoms before conception. No doubt the demands of the fetus during gestation and the loss of calcium in the milk during lactation are largely responsible. Hyperventilation and intoxication by chemicals may produce the clinical picture of tetany, but the explanation is not clear.

Tetany is seen most frequently in the winter months. The onset is, as a rule, either in the last trimester of pregnancy or during the puerperium, when the mother is nursing the baby. It is of interest that wet-nurses may develop tetany. The onset may occur in the first pregnancy but as a rule occurs late in a series of pregnancies. Symptoms may recur

in successive pregnancies, disappearing in the intervals between. Thomas [35] reported a remarkable case in which tetany developed in the second pregnancy and then recurred in each of six succeeding pregnancies. The symptoms usually appeared in the fifth month and generally disappeared during delivery. There were, however, a few mild symptoms in the postpartum period, and sometimes in the winter months when the woman was not pregnant.

Before the nature of this condition was understood, the mortality was estimated at 7 per cent. Now the symptoms should be easily controlled.[36] In cases of parathyroid deficiency, calcium salts, parahormone and dihydrotachysterol (A.T. 10) are used, although the hormone is of doubtful value. In cases of tetany due to deficient diet, calcium salts and vitamin D are effective. In cases of acute tetany calcium gluconate should be administered intravenously.

The diagnosis is rarely difficult, for the carpopedal spasms, the signs of latent tetany and the chemical changes in the blood are typical. Acrocyanosis and a form of cutaneous eruption have been described.[37] Cataracts may develop. In the type due to deficient diet there may be osteomalacia. Patients are sometimes seen in whom repeated convulsions occur when the chemical changes in the blood seem scarcely adequate to explain the seizures. It may be difficult to determine in these instances whether one is dealing with epilepsy and tetany or with tetany alone. Apparently, convulsions will occur in an epileptic patient when the blood calcium level is not low enough to induce seizures in a normal person. Taubenhaus and Engle [38] discussed this problem. In addition to epilepsy, hypoglycemia, meningitis, brain tumor and hysteria should be considered in the differential diagnosis.

### POSTPARTUM NECROSIS OF THE ANTERIOR LOBE OF THE HYPOPHYSIS AND HYPOPITUITARY CACHEXIA (SIMMONDS' DISEASE)

Knowledge of this interesting condition is largely due to the systematic and illuminating work of Sheehan, of Glasgow, and his followers.[39]

35. Thomas, H. M.: Tetany in Pregnancy, Bull. Johns Hopkins Hosp. **6**:85, 1895.

36. Anderson, G. W., and Musselman, L.: The Treatment of Tetany in Pregnancy, Am. J. Obst. & Gynec. **43**:547, 1942.

37. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, p. 1608.

38. Taubenhaus, M., and Engle, H. M.: Clinical Observations in a Case of Idiopathic Tetany and Epilepsy, J. Clin. Endocrinol. **5**:147, 1945.

39. Sheehan, H. L.: Postpartum Necrosis of the Anterior Pituitary, J. Path. & Bact. **45**:189, 1937; Postpartum Necrosis of the Anterior Pituitary, Edinburgh M. J. **45**:189, 1938. Sheehan, H. L., and Murdoch, R.: Postpartum Necrosis of the Anterior Pituitary: Effect of Subsequent Pregnancy, Lancet **2**:132, 1938; Simmonds' Disease Due to Postpartum Necrosis of the Anterior Pituitary, Quart. J. Med. **8**:277, 1939; Postpartum Necrosis of the Anterior Lobe of the Pituitary, Lancet **2**:321, 1940.

These observers have shown that it is not especially uncommon for ischemic necroses to occur in the pars anterior of the pituitary gland during delivery. Massive hemorrhage and collapse are apparently responsible, and sepsis plays no direct role. The necroses are usually small but may be large and in some instances may result in almost complete destruction of the gland. Histologically, infarctions due to thrombosis of the small veins are found. Later, one finds merely shrinking of the gland and scar formation.

Sheehan stated that in Glasgow approximately 80 deliveries each year are followed by hemorrhage and collapse. Perhaps 50 patients survive. On an average, 12 of these patients subsequently show evidences of pituitary insufficiency, and in 3 patients the symptoms are severe. Of the 30 patients who die, 22 show necrosis in the anterior lobe at autopsy.

The immediate symptoms are not always striking and may be overshadowed by the effects of hemorrhage and shock. Only in the severest cases does the patient die in coma and convulsions due to hypoglycemia. Usually the patient survives the immediate effect of the necrosis of the anterior lobe of the pituitary, though the blood sugar is reduced.

The characteristic features of pituitary insufficiency gradually become evident. During the puerperium lactation is apt to fail. There are amenorrhea and progressive atrophy of the whole genital tract. Sterility, of course, results. There are loss of libido and loss of body hair. Other symptoms are suggestive of myxedema. There may be apathy, dulness, loss of memory and sensitiveness to cold. The basal metabolic rate may be reduced to — 25 or 30 per cent. Weakness and easy fatigability are common symptoms. The fasting blood sugar averages between 60 and 70 mg. per hundred cubic centimeters. The chlorides and sodium of the blood may be low. Hypotension is observed in many cases. Sheehan insisted that, contrary to the general belief, emaciation is not constant in this condition. In only one third of his cases was the patient undernourished.

The patients are apt to die in hypoglycemic coma precipitated by intercurrent infections or as a result of prolonged undernutrition. Post mortem they show the shrinking of the hypophysis, as well as atrophy of the ovaries, the thyroid and the cortex of the adrenal gland.

The severity of the symptoms depends on the amount of the gland destroyed. Sheehan stated the belief that the symptoms will be mild if 60 per cent of the gland is lost, moderate if 75 per cent is destroyed and severe if 95 per cent is involved in the necrosis. Some women have such mild symptoms that it is possible for them to become pregnant again. There is reason to believe that pregnancy has a tendency to cause hypertrophy of the remaining glandular tissue and improvement in the patient's condition.

Our own experience with this condition has been slight. We have, however, observed the case of a young woman with severe diabetes who made a sudden recovery from her diabetes after delivery. She died in a short time in convulsions and exhibited post mortem the usual necrosis of the anterior lobe, which was exceptionally complete.

## CONDITIONS DUE TO INFECTIONS

### CHOREA GRAVIDARUM

It has long been known that an acute form of chorea, characterized by the extraordinary violence of the movements and by a not inconsiderable mortality, may occur during pregnancy. This condition has been termed chorea gravidarum. Its differentiation from the common chorea is not entirely clear, but it may be pointed out that the latter is a disease of childhood which usually disappears at puberty and which is rarely fatal.

The frequency of the chorea of pregnancy is not clearly determined. According to Willson and Preece[40], who have made an admirable study of this condition, there is reason to believe that it occurs in approximately 1 of every 3,000 pregnancies in this country. In northern European countries it seems to be more frequent than in southern Europe. A similar difference seems to exist in the Western Hemisphere, for apparently chorea gravidarum is more frequent in Canada and in the northern United States than in the South. It is a disease of young women. In a series of 666 women, the average age was 22.4 years.

Most attacks occur in the first pregnancy, though the onset may be delayed until the second or third pregnancy. There is a strong tendency for the disease to recur in subsequent pregnancies. Thus, Willson and Preece found that in a series of 99 women chorea gravidarum occurred 253 times. One woman had chorea in 13 successive pregnancies. It is stated that in approximately one half of all cases the onset is in the first trimester and that in perhaps one third the onset is in the second trimester. The disease begins abruptly as a rule. In a short time the patient is seized with violent movements of large amplitude involving the extremities, face and trunk; the paroxysms may be so severe as to toss her out of bed onto the floor and cause excoriation and bruising of the extremities. In severe cases the patient cannot take food and cannot even utter articulate sounds. In addition to the involuntary movements, there are loss of muscular tone and incoordination, as in chorea. The movements cease during sleep. Exhaustion and dehydration develop rapidly and play a major part in the outcome in fatal cases. Psychoses

40. Willson, P., and Preece, A. A.: Chorea Gravidarum: A Statistical Study of 951 Collected Cases, 846 from the Literature and 105 Previously Unreported, Arch. Int. Med. **49**:471 (March) 1932.

of a toxic-delirious type complicate certain cases. Fever is not always present, and a pronounced rise of temperature is considered an ominous sign. The blood pressure is usually normal, and none of the evidences of toxemia are seen. In approximately one third of all cases there is evidence of rheumatic heart disease. Sudden hemiplegia or occlusion of the central retinal artery may occur and is attributed to embolism. Bacterial endocarditis may develop on the rheumatic endocarditis and run its usual fatal course.

The course of this disease is variable. In a considerable percentage of cases recovery occurs ante partum. Death is said to have resulted within three days after the onset. In most cases, however, the symptoms continue during the pregnancy and for a few weeks after delivery. Occasionally the chorea continues indefinitely.

In the past, death is said to have resulted in more than 25 per cent of all cases, but at present, no doubt as a result of better nursing care and more conservative treatment, the mortality is said to be no more than 12 per cent. About half the babies are lost, however. Two cases have been reported in which the baby was said to have shown chorea for a few days after birth.

A number of postmortem studies have been made of the brain in cases of chorea gravidarum. As a rule, anatomic changes are seen, in striking contrast to the picture in chorea in which structural changes are not easy to find. It can scarcely be said that there is any general agreement about the interpretation of the lesions. There are usually congestion and edema, and sometimes scattered petechial hemorrhages. Histologic study may reveal perivascular degenerative changes, which are severest in the corpus striatum, especially in the caudate nucles. Lewy[41], who made careful studies of the nervous system in both forms of chorea, is cited as having said that the changes differ only in degree.

In the past there have been two schools of thought on the proper classification of chorea gravidarum. One group has held that it is merely chorea activated by pregnancy, and the other group has clung to the opinion that it is an entirely different disease, invariably associated with pregnancy and probably a special form of toxemia. The argument seems to have been decided at last by the work of Willson and Preece, who accumulated abundant evidence to prove that chorea gravidarum is closely associated with rheumatic infection, and hence merely a form of chorea. Some of the facts brought to light by these observers may now be given. They found that of 404 women with chorea gravidarum, over 35 per cent gave a history of previous rheumatic fever and that in 4 per cent rheumatic fever actually complicated the choreic pregnancy. About 60 per cent of the patients had previously had chorea unassociated with

41. Lewy, cited by Willson and Preece.[40]

pregnancy. It is also stated that of women who have had chorea during childhood, chorea gravidarum will develop in 25 per cent. The postmortem studies on the heart are also of great significance. Thus, of 46 postmortem examinations, evidence of rheumatic heart disease was found in 40. Acute endocarditis was the commonest finding. The close relationship of rheumatic fever, chorea and chorea gravidarum is therefore evident, and it must be accepted that pregnancy merely serves to activate the disease.

Willson and Preece also discovered evidence that a previous attack of chorea or rheumatic infection confers some degree of immunity. They pointed out that the general mortality rate is about 12.7 per cent. For women who have had chorea during childhood, however, the rate is only 7.3 per cent, and when there have been both rheumatic fever and chorea previously the rate falls to 6.3 per cent.

The diagnosis is usually evident at a glance. During the epidemic of encephalitis, however, occasional hyperkinetic types of this disease were seen which offered difficult problems in differential diagnosis. Hysterical movements must also be kept in mind. I have observed 2 cases in which illegitimate pregnancies in young girls were associated with violent choreic movements simulating closely those of chorea gravidarum. Nevertheless, in each case complete recovery occurred immediately after a frank discussion with the parents and patient.

The best treatment is conservative. It is most important to make sure that the patient receives plenty of food and fluids, and every possible effort should be made to secure as much rest as possible. Sedation, hydrotherapy and psychotherapy are all helpful. It is generally stated that pregnancy should be terminated in cases in which conservative measures are not successful, and that if this procedure is necessary it should be carried out before the patient's condition becomes too grave. It must be stated, however, that the termination of pregnancy does not always have a definitely beneficial effect, so that its value is at least open to question.

### TETANUS DUE TO POSTPARTUM INFECTION

Tetanus is a rare, but well known, result of pelvic infection during the puerperium. In most cases it is the result of an abortion in which inadequate technic has been employed.[42] In a few instances it is known to have occurred after a full term, spontaneous delivery and at least once it is recorded in a case in which no internal examination had been made.

As a rule, the symptoms begin between the sixth and the tenth day of the puerperium and run a rapidly fatal course. They do not differ in

42. Schneider, G. H.: Puerperal Tetanus After Criminal Abortion, Klin. Wchnschr. **4**:2438, 1925.

any essential from those associated with tetanus in the nonpregnant state. Death results in a very large percentage of cases, and the mortality is rarely under 90 per cent in any large series. Antitoxin has not proved effective, and even the heroic expedient of removing the uterus has been ineffectual.

Schneider's series of 111 cases collected from the literature summarizes the information available.[42]

### BACTERIAL INFECTIONS, SUCH AS ABSCESS OF THE BRAIN, SEPTIC SINUS THROMBOSIS, MENINGITIS AND MYELITIS, DUE TO POSTPARTUM INFECTION

These conditions usually result from criminal abortion but may also follow instrumental deliveries, and even normal, spontaneous deliveries. A severe pyogenic infection of the uterus results, usually due to the streptococcus. Bacteria may appear in the blood stream and be carried to all parts of the body, lodging in the nervous system, as well as in other organs.

In some instances generalized pyemia develops. Septic thrombi are formed in the cerebral veins and the dural sinuses, causing hemorrhagic infarctions of various sizes. Meningitis and miliary abscesses of the brain are invariably present. The other organs are always involved. Bacterial endocarditis is often present. Pyogenic myelitis may be associated.

In other instances, the bacterial invasion of the blood stream is of brief duration and limited extent, so that only a few metastatic infections develop. A single abscess of the brain may be the only evidence of such a transient bacteremia.

Some authorities believe that a few bacteria of low virulence may be transported to the cerebral venous system and set up a thrombotic process which behaves in every way as if it were nonseptic. This explanation has been offered for cases of cerebral infarction due to thromboses of cortical veins in which no cause can be discovered and no evidence of pelvic infection is apparent.

### POLYNEURITIS FOLLOWING POSTPARTUM INFECTION

In a few instances polyneuritis has followed a severe postpartum infection, which has usually been a result of criminal abortion. In most such cases there has been septicemia also. The common pyogenic organisms are responsible as a rule, and streptococci are usually to blame. Von Hösslin [1] recorded a number of cases of this type and pointed out that the condition develops after delivery, in contrast to the polyneuritis of pregnancy associated with vomiting, which begins as a rule in the first or second trimester and is not associated with evidences of infection.

Harris [43] mentioned a case resulting from a criminal abortion. This condition is rare at present, since the introduction of aseptic technic, and especially since the introduction of sulfonamides and penicillin.

Neuritis due to nasopharyngeal diphtheria is rare. Robinson and co-workers [44] reported an incidence of 5 cases in 50,000 deliveries. The disease does not appear to affect the course of the pregnancy. In rare instances the genital tract is the seat of a primary diphtheritic infection. Such cases are rare, and only 1 case has been noted at the Johns Hopkins Hospital. This form of the disease is generally milder and responds readily to antitoxin. Systemic symptoms and paralysis can result from neglected cases.[45]

### POLIOMYELITIS

Poliomyelitis occurs rarely during pregnancy, principally because it is a disease of the young. Aycock [46] reported the incidence of paralytic poliomyelitis as about 1 in 50,000 pregnancies and 1 in 1,000 cases of poliomyelitis. He conceded, however, that the rate varies considerably in different places and in different epidemics.

The course of the disease does not seem to be influenced by pregnancy, nor is the pregnancy interfered with by it, although this statement has been questioned by Fox and Sennett.[47] Secondary complications may arise from the motor paralyses. The paralyses of the bladder may lead to early and severe cystitis and pyelonephritis. Impaired intestinal tone may cause stubborn constipation. If the intercostal musculature is involved, respiration may become extremely difficult when the fetus nears term.

The paralysis of the mother does not affect the delivery, and even complete paraplegia causes no undue difficulty. Pregnancies in women requiring the constant use of a respirator have been carried to term.[48]

The disease may strike at any time during the pregnancy. The usual symptoms are headache, fatigue, vomiting, muscular pain and tenderness and motor weakness, involving principally the legs. The weakness progresses to paralysis, and the latter is usually ascending in type. One side

43. Harris, W.: Neuritis and Neuralgia, New York, Oxford University Press, 1926, p. 33.

44. Robinson, D.; Hardy, P., and Hellman, L. M.: The Effect of Diphtheria on Pregnancy, with a Report of Five Cases, Am. J. Obst. & Gynec. **53**:1029, 1947.

45. Beacham, W. D., and Rice, M.: Diphtheria of the Uterine Cervix, Am. J. Obst. & Gynec. **47**:417, 1944.

46. Aycock, W. L.: The Frequency of Poliomyelitis in Pregnancy, New England M. J. **225**:405, 1941.

47. Fox, M. J., and Sennett, L.: Poliomyelitis in Pregnancy, Am. J. M. Sc. **209**:382, 1945.

48. Strauss, H., and Bluestone, S. S.: Caesarean Section on a Poliomyelitic Patient Confined to a Respirator, Am. J. Obst. & Gynec. **51**:114, 1946.

may be more severely affected than the other. Occasionally the arms or chest may be affected first. The clinical picture and course are identical in the pregnant and the nonpregnant. Convulsions and unconsciousness are rare and are seen only in the terminal stages. The diagnosis rests on the demonstration of motor losses without sensory changes. Fever and muscular tenderness are present during the early stages. The cerebrospinal fluid shows mild pleocytosis, consisting of lymphocytes and a slight increase in protein.

### EFFECT OF PREGNANCY ON SYPHILIS

In contrast to the statements made in the preceding sections about the tendency of various diseases to be aggravated by childbearing, it may be said that pregnancy seems to have a beneficial effect in women with syphilis. Moore [49] stated that if a woman becomes infected just before impregnation or coincidentally with impregnation the usual signs of the disease are often suppressed completely or minimized. This effect is not confined to the early stages of the disease but is exerted to some extent throughout life, so that the mother enjoys a considerable degree of protection. Moore spoke of pregnancy in such instances as "a valuable therapeutic measure." Neurosyphilis is less likely to develop in such women who have acquired syphilis without pregnancy. The cause of this protective reaction is quite unknown.

Despite these statements, syphilis may damage the nervous system during pregnancy. Vascular lesions, meningitis, cranial nerve palsies and all the common manifestations of this disease may occur.

Unfortunately, the baby does not have such protection, and abortions, stillbirths and infants with congenital syphilis are the usual products of conception in syphilitic women. Adequate antisyphilitic treatment before or during pregnancy, however, will usually result in healthy babies.

### EFFECT OF PREGNANCY ON EPIDEMIC ENCEPHALITIS

During the ten years following the great epidemic of lethargic encephalitis a large number of papers appeared dealing with the occurrence of encephalitis in the pregnant woman. It is unnecessary to review this literature, for it was carefully analyzed by Alpers and Palmer.[2] These authors collected 37 instances in which encephalitis occurred during pregnancy or the puerperium. In those 37 cases there were 21 deaths; it is clear, therefore, that the fatality rate is definitely increased by the existence of pregnancy. There seems to be no evidence, however, that the pregnant woman is more apt to contract the disease than she would be were she not pregnant. Alpers and

49. Moore, J. E.: The Course of Syphilitic Infection in Pregnant Women, Bull. Johns Hopkins Hosp. **34**:89, 1923.

Palmer also reported 2 cases in which the disease seems to have been activated by pregnancy. In 1 of them a woman had made a complete recovery but three years later a parkinsonian syndrome developed during the last trimester of pregnancy. The other patient had encephalitis in the third month of pregnancy and recovered. However, she conceived again about nine months later, and during this pregnancy the parkinsonian syndrome developed.

The fetal mortality is also increased, for 11 babies failed to survive—from one cause or another. In 1 case it is claimed that the infant acquired the disease.

The experience of my colleagues and myself agrees in every respect with the views set forth. Ziegler, however, expressed doubt whether pregnancy influences the disease.[50]

50. Ziegler, L. H.: Follow-Up Studies on Persons Who Have Had Epidemic Encephalitis, J. A. M. A. **91**:138 (July 21) 1928.

*(To Be Concluded)*

# News and Comment

## GENERAL NEWS

**The American Board of Psychiatry and Neurology, Inc.**—The following specialists were certified at a meeting of the Board in New York, on December 5 and 6, 1949:

*Psychiatry.*—Joseph Abrahams, Washington, D. C.; Herbert Aldendorff, New York; Arnold Allen, Dayton, Ohio; Wallace G. Beckman, Palo Alto, Calif.; John Peay Bell, Louisville, Ky.; Frank Berchenko, New York; Christopher T. Bever, Washington, D. C.; Victor W. Bikales, Topeka, Kan.; James Frederick Bing, Baltimore; J. Harman Bjorklund, Philadelphia; Milton J. Blaustein, New York; Neatha V. Bolin, Waco, Texas; Joseph Cavitt Borrus, New Brunswick, N. J.; Ernest R. Bourkard, Tampa, Fla.; Frank C. Bowers, Martinsburg, W. Va.; Earl P. Brannon, Perry Point, Md.; Robert W. Buckley, Cincinnati; Edward E. Cale Jr., Natick, Mass.; A. D. Carra, Northport, New York; James D. Carter, Baltimore; James P. Cattell, New York; James Jennings Cleckley, Charleston, S. C.; Stephen Merrell Clement, Buffalo; Harry Wallace Cohen, Philadelphia; Stanley W. Conrad, Philadelphia; Irving J. Crain, New York; Joseph Benjamin Cramer, Rochester, N. Y.; Charles Herbert Cronick, Howard, R. I.; Arcangelo D'Amore, Washington, D. C.; Eugene T. Donovan, Ypsilanti, Mich.; Frank R. Drake, Washington, D. C.; Hyman J. Drell, Rockford, Ill.; Richard B. Drooz, Brooklyn; David Eden, College Park, Md.; J. Lawrence Evans Jr., Leonia, N. J.; John Sharp Ewing Jr., New Orleans; Edward F. Falsey, Brooklyn; James T. Ferguson Jr., Palo Alto, Calif.; Bernard D. Fine, Bronx, N. Y.; Malcolm Finlayson, Boston; Edward J. Folmer, New York; Thomas Lloyd Foster, Halstead, Kan.; Philip Friedland, Floral Park, N. Y.; Julius William Fryer, Hathorne, Mass.; Louis Jay Gilbert, New York; Nicolai Gioscia, Roslyn Estates, Long Island, N. Y.; David S. Harman, Chicago; William M. Harris, Perry Point, Md.; Jack Horrocks, Cleveland; John Gardner Howard Jr., Perry Point, Md.; Herman M. Hurdum, Binghamton, N. Y.; Jacob O. S. Jaeger, New York; Benjamin Jeffries, Detroit; Melvyn Johnson, Providence, R. I.; Bernard I. Kahn, San Francisco; Jacob Philip Kahn, Boston; Francis Douglas Kane, New York; Stanley S. Kanter, Boston; Irving Kartus, Topeka, Kan.; John Joseph Kavanagh, Washington, D. C.; David Melzar Keedy, San Antonio, Texas; Alex R. Kelly, Baltimore; Irlma Kennedy-Jackson, Hollyburn, British Columbia, Canada; Robert Andre Kimmich, Newington, Conn.; Sidney Kligerman, Framingham, Mass.; Stuart Clayton Knox, Los Angeles; Harry Kosovsky, New York; George Krieger, Palo Alto, Calif.; Maimon Leavitt, Topeka, Kan.; Anthony Peter Leuzzi, Yonkers, N. Y.; Howard Byron Leve, New York; Willis E. Lewis, Tuskegee, Ala.; Arthur H. Lussier, Aspinwall, Pa.; William Cochran Lyon, Gatonsville, Md.; Sterling Alexander MacKinnon, Norristown, Pa.; Anthony E. Maniscalco, Fort Custer, Mich.; Irving Allen Matzner, Van Nuys, Calif.; John B. McDevitt, New York; Joan F. McGreevy, Perry Point, Md.; James Thomas McLaughlin, Pittsburgh; Daniel Miller, Brooklyn; Angel Neftali Miranda-Rivera, Englewood, N. J.; Ellis J. Mischle, Worcester, Mass.; Whitney Hugh Missildine, Columbus, Ohio; William G. Morehouse, Columbia, S. C.; Jacob Morgenstern, Crownsville, Md.; Harold H. Morris Jr., Philadelphia; Samuel J. Muirhead, North Little Rock, Ark.; J. Martin Myers Jr., Baltimore; David John Myerson, Brookline, Mass.; Thomas A. Naclerio, New York; Felix Hugh Ocko,

Great Lakes, Ill.; Herbert L. Pariser, Columbus, Ohio; Jane Pearce, New York; John Patrick Plunkett, New Haven, Conn.; John S. Poe, New York; Paul John Poinsard, Philadelphia; E. A. Posell, Sedro-Woolley, Wash.; Douglas Hill Robinson, Trenton, N. J.; William J. Robinson, Kirkwood, Mo.; Helen B. Rogers, Tuscaloosa, Ala.; Richard Allan Rogers, Washington, D. C.; Selig J. Ross, New York; Stuart C. Runkle, Staunton, Va.; Howard H. Schlossman, New York; Edward Carl Schmidt, Milwaukee; Daniel Bradley Schuster, Rochester, N. Y.; Robert Seidenberg, Syracuse, N. Y.; John R. Shawver, Waco, Texas; *Jack Sheps, New York; Archie A. Silver, New York; Stephen M. Smith, Bethesda, Md.; David Sprague, Lakewood, Ohio; Herman D. Staples, Philadelphia; Vernon A. Stehman, Topeka, Kan.; Robert Lee Stubblefield, Denver; Fred George Swartz Jr., Grosse Pointe, Mich.; Hertha Tarrasch, Janesville, Wis.; Isadore Tuerk, Baltimore; George Arthur Tulin, New York; John R. Turiga, Beacon, N. Y.; Andre R. Tweed, Cleveland; John J. Vetter, New York; Sidney Vogel, New York; Joseph W. Vollmerhausen, Valley Stream, N. Y.; Philip Weissman, New York; George H. Wiedeman, New York; Herman E. Wilkinson, Denver; Frederic S. Willner, Central Islip, N. Y.; Virginia L. Wright, Anchorage, Alaska; Thomas Leonard Young, New Orleans; Ralph Neft Zabarenko, Pittsburgh; Anthony Zappala, Washington, D. C.; Frederick Ziegler, Los Angeles; Bernard Zuger, New York; Paul A. Zwick, Rochester, N. Y.

*Neurology.*—Herman Blustein, Chicago; *Estelle Pattillo Boynton, New York; William Fields Caveness, New York; *Irma G. Drooz, Brooklyn; Arthur L. Drew, White Plains, N. Y.; Rodney A. Farmer, Philadelphia; Gilbert H. Glaser, New York; Warren F. Gorman, New York; Lewis Michael Helfer, San Antonio, Texas; Weaver O. Howard, Tuskegee, Ala.; Saul Ray Korey, New York; Andrew J. Leemhuis, Minneapolis; Zondal R. Miller, St. Paul; Warren B. Mills, St. Louis; Martin George Netsky, New York; Geoffrey Frank Osler, New York; Daniel Sciarra, New York; Sidney Keith Shapiro, Minneapolis; Madison H. Thomas, Salt Lake City; *Joseph A. Winn, New York.

*Neurology and Psychiatry.*—William S. Chalgren, Minneapolis; Richard Webster Finner, New Haven, Conn.

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* The asterisk denotes complementary certification.

**International Congress of Psychiatry.**—The International Congress of Psychiatry, originally scheduled for October 4 to October 12, will take place September 18 to September 27 in Paris. Thirty-nine countries have already given official notices that they will participate. At the time of the congress, there will be an exhibition of psychopathologic art in the Psychiatric Center of Sainte Anne and an exhibition on history and progress of psychiatry in the Palais de la Découverte, Paris. Further information concerning the congress may be secured from the secrétaire général, Dr. Henri Ey, 1 rue Cabanis, Paris XIV°.

## POSTGRADUATE CENTER FOR PSYCHOTHERAPY, INC.

**Postgraduate Center for Psychotherapy, Inc.**—The Postgraduate Center for Psychotherapy, Inc., sponsored by the Institute for Research in Psychotherapy, Inc., and chartered by the Regents of the University of the State of New York, announces that in the spring of 1950 courses will be given in the "Work Shop" in the functions of clinical team members, technics of psychotherapy, current approaches in psychotherapy, technics of dream interpretation, technics of psycho-

analytically oriented psychotherapy and many other aspects of psychotherapy and related fields. There will be a special series of Saturday seminars, dealing with practical problems of psychotherapy. Further information and a catalogue with a complete description of all the courses may be secured from Miss Janice Hatcher, registrar, of the Postgraduate Center, 218 East Seventieth Street, New York 21.

## NOTICES

**Fellowship in Child Psychiatry.**—The Child Center of the Department of Psychology and Psychiatry, Catholic University, Washington, D. C., announces a fellowship in child psychiatry for physicians who have completed one year of internship and one to three years of psychiatric training under supervision approved for the American Board of Psychiatry and Neurology. There will be one vacancy in February 1950 and two vacancies in July 1950. Further information may be obtained from the Director of the Child Center, Catholic University, Washington, D. C.

# Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

## Physiology and Biochemistry

HISTOCHEMICAL DISTRIBUTION OF PEPTIDASE ACTIVITY IN THE CENTRAL NERVOUS SYSTEM OF THE RAT. A. POPE and C. B. ANFINSEN, J. Biol. Chem. **173**:305, 1948.

Quantitative histochemical estimations of peptidase activity in the central nervous system of the rat revealed that the splitting of *dl*-alanylglycine is accomplished more rapidly by extracts of the cerebral and cerebellar hemispheres than by similar preparations of brain stem and spinal cord. The degree of enzyme activity appears to be related to the number of nerve cell bodies present in the sample of tissue analyzed.

PAGE, Cleveland.

UTILIZATION OF ACETATE FOR THE SYNTHESIS OF FATTY ACIDS, CHOLESTEROL AND PROTOPORPHYRIN. L. PONTOCORVO, D. RITTENBERG and K. BLOCH, J. Biol. Chem. **179**:839, 1949.

Growing rats were kept on a lipid-free diet to which was added daily 1 millimol of sodium deuterioacetate per hundred grams of body weight. The isotope concentrations in the fatty acids and cholesterol indicate that 20 and 45 per cent, respectively, of the carbon atoms of these compounds are derived from acetate. About one third of the hydrogen atoms of hemin is derived from the hydrogen atoms of the methyl group of the acetic acid.

PAGE, Cleveland.

SOME PHYSIOLOGICAL AFTER-EFFECTS OF X-RADIATION. ROBERTS RUGH, J. Exper. Zool. **110**:357 (April) 1949.

Larvae of Amblystoma opacum at the same stage of morphologic differentiation (appearance of hindlimb buds) were given single doses of 25,000 or 50,000 r of roentgen radiation under various conditions of nourishment.

Neuromuscular response to tactile stimulation following irradiation was in some larvae initially greater than that of the controls, but this decreased rapidly until the third or fourth day, when there was a partial revival of the responses. Ability to respond to tactile stimulation was lost as much as forty-eight hours before cessation of the heart, and 33 per cent earlier in the larvae receiving 50,000 r than in those receiving 25,000 r. Preirradiation feeding of the larvae increased the peaks of activity and slightly prolonged the life of the larvae.

The heart rate was almost always accelerated after roentgen irradiation. In most instances the pulse curves for irradiated larvae showed a rise every three to four days, with an otherwise steady decline toward a basal average. The heart muscle continued to contract for many hours after the entire animal was unresponsive to tactile or visceral stimuli, and after the peripheral capillaries were emptied while the proximal capillaries and larger vessels were clogged with stagnant blood.

The irradiated larvae to which normally attractive food (Enchytrea) was offered refused to ingest it. This indifference to food was not due to ocular defects.

The chromatophores of the young larvae were "frozen" in the expanded state and remained dark throughout their postirradiation lives. Development both of the hindlimbs and of the external gills stopped abruptly at the time of irradiation.

All the irradiated larvae died within nine days because larval development and many of the functions of the organism as a whole were almost completely interrupted. After doses of 25,000 and 50,000 r there is a lag of a few days before loss of neuromuscular response occurs and of from six to nine days before the cardiac muscle ceases to contract.

REID, New Brunswick, N. J.

SWIMMING CAPACITY OF AMBLYSTOMA LARVAE FOLLOWING REVERSAL OF THE EMBRYONIC HINDBRAIN. S. R. DETWILER, J. Exper. Zool. **111**:79 (June) 1949.

As in a former series of experiments, reversal of the medulla end for end in Amblystoma embryos ranging from stages 21 to 23 results in a reversal of the original anteroposterior axis and the formation of a normal structure. The presumptive expanded anterior portion becomes the smaller posterior end and vice versa. This reversal occurred in all the 12 larvae studied histologically. The swimming capacity of these larvae was almost as great as that of control larvae. Hence there was functional as well as structural readjustment.

Probably, as in a previous series of experimental animals, the slightly lower average swimming scores may have been the result of the failure of the Mauthner axon to descend the cord. While the staining technic in the present experiments did not permit a study of this axon, the perikaryon was present in its normal positional relation to the vestibular nerve roots in all cases.

Reversal of the medulla probably included the dorsal portion of the otic placode, which becomes fixed at about stage 20. Those parts of the ear vesicle (macula sacculi, lagena and endolymphatic apparatus) which are derived from the dorsal half of the placode developed reversed laterality, whereas the parts derived from the ventral half of the placode exhibited mirror image twinning, as illustrated by the crista in each end of the lateral semicircular canals. This twinning of structures results from the contiguity of the rotated graft with the part of the ear field left in position.

The data show clearly that up to stage 23 internal adjustments occur so as to produce an essentially normal medulla after end to end reversal.

REID, New Brunswick, N. J.

THE ACTION OF ACETYLCHOLINE AND ADRENALINE ON FLEXOR AND EXTENSOR MOVEMENTS EVOKED BY STIMULATION OF THE DESCENDING MOTOR TRACTS. E. BULBRING, J. H. BURN and C. R. SKOGLUND, J. Physiol. **107**:289, 1948.

Using decerebrate cats with the lower part of the spinal cord deafferented, the authors studied reflex responses in the legs induced by stimulating descending spinal tracts. The effects of intra-arterial injection of acetylcholine and epinephrine on the flexion and extension reflexes, respectively, were compared. In a majority of experiments acetylcholine augmented flexion reflexes and depressed extension reflexes. In each instance epinephrine had the opposite effect. In a smaller number of experiments acetylcholine depressed flexion reflexes and augmented extension reflexes. In these experiments, also, epinephrine had an effect the opposite of that of acetylcholine. Augmentation or depression was preceded by a transient opposite phase in a certain number of instances, and epinephrine was occasionally without any effect. Slow infusion of epinephrine modified the action of acetylcholine so that (*a*) facilitation of extensor response was changed

to depression, (*b*) depression of extensor response was produced by smaller doses of acetylcholine and (*c*) depression of flexor responses was no longer seen. Acetylcholine alone (without stimulation) may cause flexion. Epinephrine abolishes this flexion and causes extension.

THOMAS, Philadelphia.

SOME EFFECTS OF NICOTINE-LIKE SUBSTANCES AND THEIR RELATION TO SENSORY NERVE ENDINGS. G. L. BROWN and J. A. B. GRAY, J. Physiol. **107**:306, 1948.

Arterial injection of nicotine and acetylcholine into the skin or mesentery of cats and dogs causes a centripetal discharge of impulses in the nerves supplying the area of injection. The response is not abolished by atropine and is not elicited by acetyl-$\beta$-methylcholine or histamine. Large doses of nicotine and large doses of acetylcholine, after physostigmine, abolish the sensitivity of the preparation to subsequent doses, but not to mechanical stimuli. The impulses probably arise through the direct chemical stimulation of some part of the terminations of the sensory nerves, although they were not obtained from single pacinian corpuscles.

THOMAS, Philadelphia.

ACETYLCHOLINE SYNTHESIS IN DIFFERENT REGIONS OF THE CENTRAL NERVOUS SYSTEM. W. FELDBERG AND MARTHE VOGT, J. Physiol. **107**:372, 1948.

The distribution of the enzyme or enzyme system which forms acetylcholine in the central nervous system of the dog was determined by examining over 40 separate regions with the use of a very sensitive quantitative method for the estimation of acetylcholine synthesis. An attempt was made to differentiate between cholinergic and noncholinergic neurons in the central nervous system. Neurons capable of synthesizing acetylcholine are assumed to be cholinergic and vice versa. With this criterion, it is found that in many instances cholinergic neurons end on neurons that are noncholinergic and that these, in turn, end on cholinergic neurons giving rise to neuron chains (motor or sensory), consisting of alternating cholinergic and noncholinergic links.

THOMAS, Philadelphia.

## Psychiatry and Psychopathology

MULTIPLE ACCIDENTS AS NEUROTIC SYMPTOM. CICERO C. DE SOUSA, Arq. neuro-psiquiat. São Paulo **5**:155 (June) 1947.

A white man aged 24, married, a mechanic, was studied because of a history of seventeen accidents during a period of thirteen months. There was no evidence of physical defect or neurologic disorder which could predispose to such accidents. There was no psychosis or mental deficiency. The mental examination showed an evident neurosis with anxiety, phobias, irritability and envy. A Rorschach test confirmed the presence of a neurosis. The author believes that the proneness to accidents was a neurotic symptom resulting from unresolved intrapsychic conflicts. The accidents were considered an expression of self-castigation and castration as punishment for suppressed Oedipus desires. The author believes that in this case the question of secondary gain in illness was of little significance.

N. SAVITSKY, New York.

PSYCHOGENESIS OF THE PEPTIC ULCER. L. P. AVANCINI, Wien. klin. Wchnschr. **61**:104 (Feb. 18) 1949.

A few hours after having assisted at gastric resection for a perforated duodenal ulcer, a medical student aged 20 began complaining of epigastric discomfort. During the night the complaints increased, and vomiting appeared. He was admitted

to the hospital the next day, where he was seen by the author in the course of the afternoon. The patient was thin and pale, with typical vegetative stigmas. The epigastrium was tender, but there was no rigidity; the white cell count was 7,000. During the next three hours the clinical picture remained unchanged except for an increase in white cells to 10,000. The free hydrochloric acid value for the vomitus was 100 per cent. A laparotomy was performed. The only pathologic finding was the edema of the posterior aspect of the prepyloric region of the stomach. When the stomach was opened, it was found that the entire prepyloric area was the seat of numerous hemorrhagic erosions. Since it was impossible to foresee how far these changes might progress, a gastric resection was performed. The postoperative course was uneventful. Microscopic studies showed typical hemorrhagic erosions. It is to be noted that the patient had never before had gastric complaints.

The time relation between participation in a major surgical procedure and the appearance of the first gastric symptom supports the psychogenic theory of ulcer. The high acidity value of the gastric juice is also in favor of that view.

MASON, New York.

## Meninges and Blood Vessels

ULTRAVIRAL MENINGITIS AND ENCEPHALOMYELITIS. ETIENNE KORNYEY, Encéphale **38**:266, 1949.

Kornyey has been engaged in the task of delimiting the diseases of indubitable virus etiology and the diseases in which, until very recently, such an origin has been purely hypothetic. In the latter group he claims to have found some diseases for which he could demonstrate a microbial agent. For others an allergic cause has been favored by a large number of authorities. He discusses diseases of the leptomeninges, polioencephalomyelitis and some diseases recently regarded by Pette as panencephalitis.

Among the benign meningitides, he found a form which appears to be characterized by persistence for about four weeks of the pleocytosis, even in cases in which the clinical symptoms existed only for several days. This type of evolution appears to be characteristic of meningitis due to an ultravirus; at least it represents one of its typical forms of evolution. By this sort of prolonged course the benign meningitis is differentiated from the meningitic forms of poliomyelitis, in which the pleocytosis usually lasts only four to eight days. In the diagnostic use of the information furnished by the cerebrospinal fluid in both benign meningitis and poliomyelitis, one must take into account the stage of the disease during which the fluid was obtained. The author reserves his opinion as to whether there also exist atypical cases of viral benign meningitis complicated by parenchymal lesions. Nevertheless, it appears certain that papilloretinitis, even of a severe degree, may complicate such disease.

There is need of a revision of the concept of neurotrophy with regard to the viral diseases of the parenchymal nerve tissue. The diseases of this group constitute a series, beginning with poliomyelitis, characterized by an elective gangliocellular destruction, and ending with certain encephalomyelitides, in which there appears to be no essential separation of the histologic process in the white and in the gray matter. Abortive poliomyelitis should not include those cases in which the disease is not accompanied with pleocytosis. In the initial stages of poliomyelitis, the prognostic value of the relationship between polymorphonuclear cells and lymphocytes in the cerebrospinal fluid is limited, but not entirely negligible if one takes into account the stage of clinical evolution. In view of the regular partition of the histologic process in the disease, one should exercise a prudent reserve concerning atypical forms, particularly when the symptoms of a cerebral lesion permit the exclusion of poliomyelitis.

ZINKIN, New York.

VASCULAR HEADACHE CAUSED BY ARTERIALGIA OF THE SUPERFICIAL TEMPORAL ARTERY AND ITS SURGICAL TREATMENT. F. KAJTOR, Monatsschr. f. Psychiat. u. Neurol. **118**:1 (July) 1949.

Kajtor proposes the use of arterial resection in cases of vascular headache produced by arterialgia of the superficial temporal artery. The treatment is considered fairly specific when cases are selected on the basis of their response to the procaine infiltration test and the simultaneously administered histamine test. The vessel in question is infiltrated with procaine hydrochloride, and 0.05 to 0.1 mg. of histamine is injected intravenously. In some cases, the injection of histamine produces pain. In cases in which the characteristic response does not occur, arteriectomy is preferred, and complete and permanent relief is effected by the operation. When several vessels, usually branches of the external carotid artery, are involved, the provocative tests are applied to each branch. Generally, the resection of the vessel should be carried out as far proximally as possible. Unilateral arteriectomy was performed in 19 cases, with relief of pain in 11 cases, various degrees of improvement in 4 cases and alleviation of pain in 4 cases. Of 7 cases in which a bilateral vascular resection was done, there was complete remission of pain in 1, considerable improvement in 2 and no change of symptoms in 4. The negative results were attributed to poor selection of cases, since the provocative tests had been only partially administered. It is not necessary to distinguish the migrainous, arteritic, histaminic, traumatic and psychogenic types of headaches; the sole criterion is the response to the procaine infiltration and histamine injection tests.

The vascular pain (arterialgia) is thought to be related to a segmental paroxysmal dysrhythmia of the vasomotor innervation in parts of the distribution of the carotid artery on either one or both sides. Furthermore, there is a unique sensitization of the arteries to histamine, with production of the vascular pain. Resection of a portion of the artery abolishes the abnormal vascular pulsations and interrupts the pain-sensitive fibers running along the arteries. PISETSKY, New York.

MENINGITIS DUE TO ESCHERICHIA COLI TREATED WITH STREPTOMYCIN. S. W. TAUB, Harefuah **34**:119 (May 16) 1948.

A man, aged 21, who was shot in the left side of the abdomen was brought to the hospital in shock. Roentgenograms showed that the bullet was lodged in the region of the sacrum. At operation the abdominal cavity was found to be filled with blood, with bleeding from the mesentery and two tears in the small intestine and the sigmoid. Though 1,000,000 units of penicillin was given after operation, the temperature continued to rise. On the fourth postoperative day the patient complained of headache and the neck was found to be stiff. He was somnolent. On the tenth postoperative day there was clearcut meningitis. On the eleventh day lumbar puncture showed cloudy fluid under high pressure, with many cells; injected iodized oil stopped at the first sacral segment. The first and second laminas were removed; an epidural infection was found, which penetrated into the subarachnoid space, and a bullet in the epidural space was removed. Escherichia coli was cultured from the spinal fluid and the epidural pus. Treatment with streptomycin was begun, 3 Gm. being injected intramuscularly each day. In seven days the spinal fluid was sterile, and the dose was reduced to 1.5 Gm. daily. The patient became worse, with reappearance of the organisms in the spinal fluid. The dose was again increased, and on the thirteenth day the spinal fluid was again sterile. Seven days later Esch. coli was found in the pus at the operative site. Streptomycin was continued until 59 Gm. had been given. The patient was able to leave the bed forty days after he was wounded. He complained of dizziness,

and the caloric responses were diminished. After seventy days he left the hospital in good condition. The decrease in caloric responses was considered to be due to the streptomycin.

N. SAVITSKY, New York.

## Diseases of the Brain

CEREBRAL THROMBOPHLEBITIS AND FIBRINOGEN B. GILBERT PHILLIPS, J. Neurol., Neurosurg. & Psychiat. **11**:263 (Nov.) 1948.

Phillips reports 7 cases of thrombophlebitis involving the superficial cerebral veins and the dural venous sinuses. The diagnosis was established on the basis of the following common factors: increased intracranial pressure with marked papilledema; external hydrocephalus with accumulation of subarachnoid fluid; normal ventricles; presence of a septic focus, usually about the head but sometimes in a remote situation, and a tendency toward spontaneous resolution of the symptoms. In 6 of the cases blood tests revealed the presence of fibrinogen B. The intensity of the latter reaction fluctuated rapidly throughout the course of the illness. In the opinion of the author, the therapeutic attack should include removal of the infective focus, inactivation of the circulating prothrombin in the blood by intravenous injection of heparin, reduction of prothrombin formation in the liver with dicumarol and repeated spinal drainage to decompress the optic nerves when vision is rapidly deteriorating.

N. MALAMUD, San Francisco.

EPILEPTIC RESPONSE TO PERIPHERAL INJURY. GERALD PARSONS-SMITH, J. Neurol., Neurosurg. & Psychiat. **11**:267 (Nov.) 1948.

A man aged 41 without previous history of epilepsy sustained a crushing injury to his left hand. Examination revealed signs of damage to the terminal cutaneous branch of the radial nerve. Twenty-four hours later the patient experienced a "fit," lasting one-half minute and characterized by a tickling sensation, stiffening and adduction and flexion in the thumb and first two fingers of the affected hand, followed immediately by a series of jerky movements of the whole arm. The attacks recurred two or three times daily during the next week. Knocking or hurting the hand did not precipitate the attack, but the patient was able partly to control the seizure by restraining the limb. Ten days after the injury he experienced a similar attack, which spread to involve the face and was followed by an episode of loss of consciousness. Neurologic examination later revealed only signs of radial palsy. A roentgenogram of the limb muscles demonstrated the presence of calcified cysts, but there were none in the skull. The cerebrospinal fluid contained 46 cells per cubic millimeter and 50 mg. of protein per hundred cubic centimeters. An electroencephalogram showed persistent low voltage fast activity in all leads. A diagnosis of cerebral cysticercosis was made. Subsequent electroencephalographic examinations reaffirmed the dysrhythmia. This was not affected when a series of sensory stimuli were tried to the impaired hand. With increasing doses of phenobarbital, the "fits" gradually cleared up. The author is of the same opinion as other investigators that in such cases of epilepsy associated with peripheral nerve injury there may be some abnormality in the reflex arc on the afferent side between the periphery and the cortex. The stimulus which provokes this epileptic response is usually of special type and may excite epileptic symptoms if the corresponding part of the cortex is in an unstable state.

N. MALAMUD, San Francisco.

AIR EMBOLISM OCCURRING DURING ENCEPHALOGRAPHY. ARTHUR B. KING and FRANK J. OTENASEK, J. Neurosurgery **5**:577 (Nov.) 1948.

King and Otenasek report 2 cases of death from air embolism during air encephalography. The first was that of a man aged 54, in good physical condition, who became cyanotic and ceased breathing after the injection of 140 cc. of air into the subarachnoid space. Efforts to revive him were futile. At autopsy, twelve hours after death, air was seen in the veins throughout the body. The right auricle contained air under pressure, and all the chambers of the heart contained bloody froth.

The second case was that of a child aged 6 months, who suddenly ceased breathing after 50 cc. of air had been introduced. The spinal fluid removed was blood tinged at the end of the procedure. Efforts at revival were unsuccessful. Autopsy revealed bloody froth in the heart, and when the right auricle was opened there was an escape of free gas. The site of entry of the air was not found.

The authors believe that the most likely site for the air to enter the venous system would be a tear of a small vessel of one of the dural sinuses, thus allowing subarachnoid air to enter the vascular system.

TOZER, Philadelphia.

DISSEMINATED SCLEROSIS IN SOUTH AFRICA. GEOFFREY DEAN, Brit. M. J. **1**:842-845 (May 14) 1949.

Dean believes that there is probably some relation between multiple (disseminated) sclerosis and sway-back disease, since Campbell and co-workers found 4 cases of the former condition among 7 research workers studying sway-back. Furthermore, Dean was able to find only 5 cases of multiple sclerosis among 2,400,000 white persons in South Africa, where sway-back is equally uncommon. Since copper sulfate is known to be effective in the prophylaxis and treatment of sway-back, Dean suggests that it be tried in the treatment of multiple sclerosis.

ECHOLS, New Orleans.

MENINGEAL LESIONS IN A CASE OF ATROPHIC DEMENTIA. J. DELAY and P. SIZARET, Encéphale **38**:324, 1949.

The clinical and encephalographic findings in this case had previously been reported in 1946. The present report concerns the postmortem findings. Clinically and encephalographically, the case was one of presenile dementia of the Pick or Alzheimer type. The course was marked by episodes of violent agitation; the dementia was steadily progressive and severe. The patient was 54 years of age at the time of his death. Neurologically, only amimia, rigidity and generalized hypertonia were noted. The outstanding observation at autopsy was the large, thick and slightly adherent area of pachymeningitis on the concave, internal surface of the dura mater. The patch did not adhere to the cortex and covered the two prefrontal lobes, which were very atrophic. The plaque of meningitis seemed to be formed at the expense of the leptomeninges. Elsewhere the meninges were normal. The pia mater was not adherent. The brain weighed 990 Gm. after preservation in formaldehyde. Inspection revealed marked prefrontal atrophy with widening of the sulci and dilatation of the ventricles, particularly the frontal horns. The vessels were not sclerotic, and there were no focal lesions or lacunas. All choroid plexus was normal. Microscopically, the area of pachymeningitis consisted of a layer of extremely dense fibrous tissue, abundant collagenous material and few connective tissue cells; the plaque was moderately vascularized and seemed to have developed very gradually. Iron was present in the preparation.

The frontal cortex revealed no inflammatory lesions. Microscopic examination showed marked chronic cellular atrophy, numerous large zones which were almost completely acellular and many damaged pyramidal cells. The third, fourth and fifth layers of the cortex showed considerable edema. No Alzheimer lesions or senile plaques were observed. The other cortical areas showed fewer alterations. The occipital cortex had undergone only slight changes. The caudate nucleus showed some vacuoles, but all the lesions were much less pronounced than in the occipital area.

The case appeared to be one of simple presenile atrophic dementia without inflammatory or vascular pathologic change. The only peculiarity was the area of pachymeningitis covering the atrophic areas. A search of the literature revealed 11 similar cases of senile or presenile atrophy associated with meningeal lesions. In none was there a history of meningitis—inflammatory, infectious or traumatic. The pia mater was never adherent to the cortex. The meningeal lesion almost exclusively involved the external leaf of the leptomeninges. Frequently there were signs of hemorrhage, usually old, sometimes recent. The pachymeningitis usually covered the atrophic areas of the cortex. The authors agree with Pette in believing that the meningeal lesion is secondary to the atrophy of the cortex and has a progressive evolution. It is a consequence of the cortical atrophy.

There are no special diagnostic signs or symptoms which may lead one to suspect the existence of the pachymeningitis. Perhaps the variability of the symptoms together with the periods of agitation may be of some help. Roentgenograms and air studies are useful, particularly in cases of subdural hematoma. The authors stress the frequency and importance of meningeal lesions in degenerative diseases of the brain. Such lesions raise interesting problems of pathogenesis and diagnosis, both from the theoretic and from the clinical aspect.

ZINKIN, New York.

NERVOUS SYSTEM DISEASES AND PROBLEMS OF HEREDITY. LUDO VON BOGAERT, Acta neurol. et psychiat. Belg. **48**:339 (Aug.) 1948.

Von Bogaert concludes that heredofamilial diseases are an expression of one and the same organogenetic disorder whether they occur early or late in life. The time of onset and the type of involvement may vary in individual cases. It is possible to differentiate pure abiotrophic diseases, metabolic degenerative disorders, congenital malformations and blastomatous dysplasias. All of these cannot be explained on mendelian inheritance alone and may reflect chemical and other metabolic changes.

DEJONG, Ann Arbor, Mich.

## Diseases of the Spinal Cord

POLIOMYELITIS: EARLY DIAGNOSIS AND EARLY MANAGEMENT OF ACUTE CASES. JOHN R. PAUL, Ann. Int. Med. **30**:1126 (June) 1949.

Paul is concerned with the early aspects of the diagnosis and therapy of poliomyelitis. He stresses the term "early" as meaning that period often before the patient reaches the hospital, because at that stage of the illness the critical period has usually already passed. He quotes Russell's statement that "the battle to decide the fate of the spinal cord cells is probably over before the paralysis is detected."

There has been some change in the clinical picture and in the epidemiology of the disease during the past years. The age of the average patient with poliomyelitis tends to be older than it was a generation ago. In this sense the disease is no longer "infantile paralysis." There is no explanation for this shift in the behavior of the disease other than that it is due in part to shifts in the age composition of the popula-

tions involved. The clinical implication, however, is clear in that adult poliomyelitis is becoming commoner. Moreover, cases of the nonparalytic disease are more commonly reported, but this does not necessarily mean that there is a real increase in the incidence of this type; rather, the increase may be attributed to the fact that these cases receive more clinical attention than they did heretofore.

Paul stresses the fact that the symptomatology of acute poliomyelitis differs in different age groups and that the so-called diphasic course, which is classic for children, is certainly less common in persons above the age of 14 years. Pain in the back and an insidious onset are more apt to occur in patients past the age of 15. There are many cases, particularly among the older adolescents and the younger adults, in which the disease has been called the "straggling type of poliomyelitis." This rather poor term expresses how the patient drags along for a few days, with doubt as to the diagnosis. For early and accurate diagnosis, one must not depend on the typical symptoms presented by the small child if one is to detect the disease in older children and in adults.

One cannot be didactic about the treatment of poliomyelitis, particularly in the earlier stages. During epidemics the most astute clinician cannot determine during the first hours or days whether a given patient whose initial symptoms are limited to sore throat, headache, fever and vomiting will or will not have paralysis. However, the physician's responsibility lies in the management of patients of any age who may be in the early stages of abortive or paralytic poliomyelitis. Paul states that all persons with brief febrile illnesses occurring during an epidemic of poliomyelitis should be regarded with suspicion and their physical activities curtailed, and that they should be treated more cautiously than usual and kept under observation about ten days. There is, moreover, a theoretic public health aspect of the nonparalytic case. The degree of paralysis or the severity of involvement of the central nervous system bears no direct relation to the excretion of virus in the mouth or the intestinal tract.

"It is not necessary for the attending physician to make a *public diagnosis* of poliomyelitis in order to observe a suspicious case for a week or 10 days. Indeed the physician may not care to mention the possibility of poliomyelitis to the family, for families are prone to be apprehensive to the point of hysteria during an epidemic and anything which minimizes commotion is desirable. The local health officer may also object if the diagnosis is made too freely or made in the absence of orthodox diagnostic criteria. But this caution does not detract from the desirability of *observing* early and questionable cases most carefully for the development of 'secondary phase' signs, and of regulating their physical activity."

Paul does not recommend that all nonparalytic patients be hospitalized; the decision as to hospitalization of patients with the milder disease varies in different places and during different epidemics and should certainly depend on the individual patient, the local facilities for hospitalization and the facilities for observing the patient at home. The author states that a special isolation hospital is not necessary for poliomyelitis patients and that general hospitals can care for them and should accept their community responsibility to do so.

There is no specific therapy. Antipoliomyelitis serum, chemotherapy and antibiotics do not seem to offer much. Strong analgesics are not very effective in the control of the pain, and the application of moist heat remains the most practical method of combating pain. Paul has had little direct personal experience with the use of neostigmine and curare, and he is inclined to regard the use of both these drugs as still in an experimental stage. He goes on to state, "Any physician who has much to do with the clinical responsibilities in this disease knows full well of the pressure which is brought to bear by parents and well meaning friends, to

do something definite, something positive or even new and spectacular in the way of treatment. My own feeling is that all meddlesome forms of therapy should be avoided because of their potential traumatic effect. Therapy which includes the use of strong purgatives seems to be contraindicated."

Many aspects of therapy fall within the province of the orthopedist and belong in the category of after-care. Management of the bulbar form of the disease, in which the air passages must be kept as free from secretions as possible by postural drainage, suction and, as a last resort, tracheotomy, presents special problems, as does the use of the respirator.

In conclusion, Paul stresses the fact that, certainly during epidemics at least, it is expected that a team can best perform the tasks of management of poliomyelitis patients. He thinks that this team may best be composed of an orthopedist, a physical therapist, specially trained nurses and others. The physician is to remain in charge of the situation until the disease has definitely gone into the stage of after-care, and he should be on the alert to guard his patient from unnecessary trauma, exertion and, above all, meddlesome therapy. The early treatment of poliomyelitis calls for an alert physician, whose major responsibility is to guard his patient and be ready for any serious emergency.

GUTTMAN, Wilkes-Barre, Pa.

## Peripheral and Cranial Nerves

TIC DOULOUREUX IN SIX MEMBERS OF THE SAME FAMILY. E. CASTANER-VENDRELL and L. BARRAQUER-BORDAS, Monatsschr. f. Psychiat. u. Neurol. **118**:77 (Aug.) 1949.

The authors record the occurrence of trigeminal neuralgia in 6 members of the same family, representing four generations. The case of a man aged 67 with a history of paroxysmal pain in the right maxillary region of fifteen years' duration is reported. Frazier's operation of root resection relieved the pain. A study of his family revealed that 2 sisters also had the disorder; one, aged 73, was also cured of her pain by this operation. The patient's mother; maternal grandmother, and one of his nieces, the daughter of his second brother, also suffered from tic douloureux. The right side was involved in all cases.

PISETSKY, New York.

MOTOR VARIANTS OF HERPES ZOSTER. CARLOS A. BARDECI, Rev. Asoc. méd. argent. **63**:326 (July) 1949.

Bardeci reports 3 cases of herpes zoster in adults aged 38, 68 and 78, respectively. One patient had dementia paralytica, and another, carcinoma of the uterus; both conditions were considered coincidental to the herpes. In all 3 cases motor paralysis developed soon after the appearance of a typical vesicular eruption, the paralysis and atrophy involving the cervicobrachial distribution in all 3 cases. In 2 cases the upper roots of the brachial plexus were mainly involved; in the third the lower roots were involved, with a Klumpke-Déjerine syndrome. In 2 cases the areas involved by the cutaneous lesions corresponded to the motor paralysis. In 1 case the motor pareses were more widespread than the sensory changes. In 2 of the patients the paralyses cleared up in three and four months, respectively. There were no fibrillations. The motor paralysis was probably due to direct extension to the anterior horns, and perhaps the motor roots.

N. SAVITSKY, New York.

## Treatment, Neurosurgery

SUBDURAL EMPYEMA. WILLIAM S. KEITH, J. Neurosurg. **2**:127 (March) 1949.

Keith reports 7 cases of subdural empyema treated by antibiotics and drainage. In 6 of the 7 cases, infection entered the subdural space via the paranasal sinuses. In 5 of the reported cases the leg area had become involved before the arm area by extension of the suppurative process over one or both sides of the falx cerebri.

Penicillin and the sulfonamides may prevent the formation of subdural empyema in some cases and modify the severer cases so that surgical treatment can be instituted.

When the diagnosis is suspected, burr holes should be made at the suspected site, usually the posterior frontal area near the midline. Both sides should be explored if necessary. If empyema is found, surgical drainage is employed. The bone is removed, the dura is opened, and drainage is instituted by soft Penrose type drains. Penicillin may be injected into these drains in the subdural space. as well as given intramuscularly. All of the author's 7 patients survived with the above treatment.

TOZER, Philadelphia.

LIVER EXTRACT, FOLIC ACID, AND THYMINE IN PERNICIOUS ANEMIA AND SUBACUTE COMBINED DEGENERATION. TOM D. SPIES and ROBERT F. STONE. Lancet **1**:174 (Feb. 1) 1947.

The authors find that synthetic folic acid and synthetic thymine will neither prevent the development of subacute combined degeneration in addisonian pernicious anemia nor relieve it once it has developed, whereas frequent parenteral injections of a potent liver extract are helpful in this condition, both in prevention and in relief.

MADOW, Philadelphia.

TREATMENT OF MOTOR DISTURBANCES. OTTO MARBURG, Confinia neurol. **9**:365, 1949.

Marburg identifies three components in motor disturbances: kinetic, tonostatic and dynamic. The kinetic component is represented by pyramidal disturbances and is improved with carbachol U. S. P. The tonostatic component, predominant in paralysis agitans, is treated with magnesium gluconate given by mouth. Only in cases in which there is a disturbance of the dynamic component, as in myasthenia, will neostigmine be effective. Roentgen therapy is suggested for use in intermittent claudication.

FOLEY, Boston.

UNILATERAL PREFRONTAL LOBOTOMY FOR RELIEF OF FACIAL ANESTHESIA DOLOROSA AND ATYPICAL FACIAL NEURALGIA. GERMAN HUGO DICKMANN and DORA T. BIELSA, Prensa méd. argent. **36**:1483 (August 5) 1949.

Dickmann and Bielsa report 2 cases of facial pain in patients aged 74 and 50, respectively. The older patient had a history of recurrent pain in the face for thirty-four years. Injection of alcohol did not result in improvement but added annoying paresthesias. The younger patient had an atypical refractory facial neuralgia. Pain and paresthesias continued to recur after section of the fibers of the fifth nerve distal to the gasserian ganglion. Satisfactory alleviation of pain and paresthesias followed unilateral prefrontal lobotomy on the affected side in both patients.

N. SAVITSKY, New York.

SPECIFIC PROPHYLAXIS OF POSTDIPHTHERITIC PARALYSES. E. LORENZ, Wien klin. Wchnschr. **61**:12 (Jan. 7) 1949.

During a period of one and a half years, diphtheria antitoxin was administered intraspinally in addition to the intramuscular or the intravenous route. The frequency, severity and duration of paralyses were definitely decreased as compared with the corresponding findings for a control group of children who did not receive the antitoxin intraspinally. The children given intraspinal treatment showed an incidence of neurologic involvement of 43.2 per cent and no neurologic mortality, as compared with an incidence of involvement of 60.9 per cent and 8 fatal cases for the control group. The duration of the paralytic phenomena was reduced by half.

MASON, New York.

DIATHERMY AND SHORT WAVE TREATMENT OF THE MIDBRAIN. E. DROBEC, Wien. klin. Wchnschr. **61**:26 (Jan. 14) 1949.

The importance of the midbrain in the endocrine, vegetative and psychic spheres is well known. An attempt was made to influence various conditions theoretically associated with the diencephalon through diathermy or short wave treatments. Biparietal lead electrodes were used. In 2 cases of endocrine disorders with overweight, 1 of psychic origin and the other resulting from physical trauma, the results were good. Remarkable improvement followed only a few short wave treatments in a case of Raynaud's disease. In a case of angioneurotic (Quincke's) edema following encephalitis there was regression of the chronic edema. In 2 cases of postencephalitic psychic sequelae (depressive and neurasthenic features in 1, neurasthenic and obsessive-compulsive neurosis in the other) definite improvement occurred. Cerebral vascular disturbances (migraine, postencephalitic syncopes, vascular lesion with involvement of the internal capsule) have also greatly benefited. Drobec emphasizes the possibility of research on acute and chronic encephalitis, epilepsy and glaucoma.

The equilibrium of the midbrain is reestablished through intracellular regeneration and an improved blood supply. The stimulating effects of the heat is obvious; on the other hand, there is the possibility of a specific action of high frequency currents. Microscopic changes in the capillaries have been previously demonstrated; chemical and colloidal changes may follow.

In order to establish whether there is involvement of the pituitary and midbrain, the urinary function is studied, using Volhard's method. In cases of such involvement there is apparent a definite influence of diathermy or short wave therapy on the results of that test, which is based on the diuretic and antidiuretic action of hormones of the pituitary gland.

MASON, New York.

## Encephalography, Ventriculography, Roentgenography

VERTEBRAL ANGIOGRAPHY. O. SUGAR, L. B. HOLDEN and C. B. POWELL, Am. J. Roentgenol. **61**:166 (Feb.) 1949.

The authors describe a technic for percutaneous injection of the vertebral artery with the patient under anesthesia, 35 per cent iodopyracet U. S. P. (diodrast®) being used as the contrast medium. Stereoscopic lateral roentgenograms of the skull are made routinely; occasionally an anteroposterior view is taken.

Five cases illustrate the type of information obtained with this procedure. In 2 cases basilar aneurysms were demonstrated before operation. An angiogram in a third case, with traumatic carotid artery–cavernous sinus fistula, showed collateral

circulation of the entire cerebrum. In another case, of hypertensive vascular disease and spastic hemiparesis, a diagnosis of vertebral-basilar anteriosclerosis was made from the vertebral arteriogram. The vertebral and basilar vessels are narrow, and there were irregularities of diameter of the extracranial portions of the vertebral artery. The intracranial branches were sparse and the terminal vessels exceedingly tenuous. The vertebral angiogram in the fifth case revealed vascular abnormalities, which were shown to be due to metastatic disease of the thalamus.

In over twenty attempts to inject the vertebral artery, there were only two failures; in both instances a vertebral vein was injected.

Among the minor complications were two urticarial reactions to iodopyracet. These were readily controlled by ephedrine. In 1 case a brachial plexus root neuralgia developed, the nerve roots having been struck during manipulation of the needle. The most serious complication was a Brown-Séquard syndrome from below the neck, on the same side as the injected vertebral artery. Fortunately, recovery was gradual and complete. No satisfactory explanation of this complication could be given.

TEPLICK, Philadelphia.

# Society Transactions

## CHICAGO NEUROLOGICAL SOCIETY

*Paul C. Bucy, M.D., President, Presiding*
*Regular Meeting, March 9, 1948*

**Glioblastoma Multiforme: A Study of 211 Verified Cases.** Dr. Loyal Davis, Dr. John Martin, Dr. Stanton L. Goldstein and Dr. Moses Ashkenazy.

The authors studied 211 patients with glioblastoma multiforme, verified microscopically. In a series of 860 verified intracranial tumors there were 455 gliomas. The 211 tumors diagnosed as glioblastoma multiforme constituted 29.5 per cent of the total number of intracranial tumors and 46.4 per cent of the gliomas. All but 8 of these patients were followed to the time of death. Of the group of 211, 24 patients were moribund when admitted to the hospital and died before any surgical procedures were carried out. The diagnosis was verified by autopsy. On the remaining 187 patients 225 operations were performed, and, of these patients, 77 died in the hospital within one month after operation. The cause of death in many cases was the direct result of the operation, but any death within one month after operation, regardless of the cause, was considered an operative death. In 8 cases of verified glioblastoma, ventriculographic examination was performed, and the patients died before any surgical attack on the tumor was made. Of the 110 patients who survived operation, 41 lived six months or less; 38 survived seven to twelve months; 12 survived one to two years, and 11 survived longer than two years. The longest survival time in the series was forty-one months.

Division of the tumors into three pathologic groups (angionecrotic, multicellular and magnocellular) according to the method described by Busch and Christensen was only partly successful, for in many cases there was no clearcut differentiation of the types. This was true also of the attempt to distinguish angiothrombotic and angioproliferative groups. It appeared, however, that patients with the proliferative type survived for a significantly longer period after operation.

Of the 4 patients in the 3 to 10 year age group, none survived operation; the 2 patients over 70 years old were moribund on admission and died without operation. Of 19 patients in the 61 to 70 year group, none lived for more than one year.

There was no significant difference in survival times for the tumors of the frontal, parietal and temporal lobes, respectively. The operative mortality was higher when more than one lobe was involved or when the tumor extended into the opposite hemisphere.

In addition to the 211 tumors studied, 14 were originally classified as glioblastoma multiforme and on several restudies were verified as such. Because of the unusually long survival periods, these tumors were critically and repeatedly restudied, with the final diagnosis of astrocytoma (8 cases), medulloblastoma (3 cases), oligodendroglioma (1 case), spongioblastoma unipolare (1 case) and melanosarcoma (1 case).

In summary, more than one fifth (23) of the patients who survived operation lived more than one year, and one tenth (11), more than two years; during this time the patients were not only more comfortable than they had been, but were

able to fulfil both economic and social obligations. The survival rate was higher for the angioproliferative than for the angiothrombotic group. Patients in the extreme age groups had a poor prognosis. The operative mortality was higher if more than one lobe was involved or if the tumor extended into the opposite hemisphere. When the bone flap was removed, there were fewer operative deaths than when only the usual decompression was done. There was a longer survival period for the patients who received adequate roentgen radiation. Definite microscopic differences before and after roentgen irradiation were noted in some tumors. Seven tumors showed a transition from a more benign glioma to gliomablastoma multiforme during treatment.

DISCUSSION

DR. IRVING C. SHERMAN: I wonder whether the authors would comment on the damage to the patient in radical resection of tumors on the left side.

DR. PERCIVAL BAILEY: I can think of no other intracranial neoplasm for which the methods of management vary so widely as for glioblastomas. The reason is obvious. The results are bad no matter what the management. Previous attempts to subdivide this group have not proved useful. Whether such an attempt will give better results remains to be seen.

I have been interested in the preoperative diagnosis of these tumors by arteriography. It is possible to make this pathologic diagnosis by arteriography in about 75 per cent of cases, and I believe it would be possible in a larger number if one were able to take serial plates during passage of the dye. My colleagues and I are now trying to develop a plate changer that will enable a picture to be taken every second; if this can be done, I believe it will be possible to make a diagnosis in 85 per cent of cases or more and to determine where the tumor is located in the brain. Suppose that one can do it, what advantage is gained? Obviously, not a great deal. Even if the tumor is confined to one lobe of the brain and the lobe is extirpated, the patient dies within a year through recurrence. I have a case in which I extirpated all the cortex and part of the basal ganglia of one hemisphere, in 1929. I am not proud of that case. The patient has been a charge and a burden on the government and on me ever since. Perhaps one might attempt such an operation if the patient were wealthy and did not need to earn his living. Possibly, therefore, we shall not gain a great deal by diagnosis of these tumors by arteriography except to avoid useless operation.

Whenever I am able to make the diagnosis, my attitude is to do a decompression and give roentgen radiation—intensive radiation, sufficient not only to check the growth of the tumor, but also to cause degeneration of the brain, so that the patient reacts as with a lobotomy and dies without pressure and without anxiety. So far as I know, there is not a chance that he will survive anyway, and I think that this is a better method of managing such cases than to wait until there is a recurrence and operate again.

DR. LOYAL DAVIS: There is no question that the surgical treatment of the glioblastoma is a difficult problem. That is recognized by every neurologic surgeon. I feel, however, that because the problem is difficult and the results are discouraging, one should make greater efforts to solve it. It constitutes the most serious challenge to the neurologic surgeon. If the surgical treatment of cancer elsewhere in the body—gastric cancer and breast cancer—had been regarded with the same pessimism, it would not have progressed to the present encouraging status. Certainly, neurosurgeons do not have the answer now; but they will never have the answer if these tumors are not attacked by every new method of treatment available.

It is necessary for surgeons to discuss their results honestly and frankly, with perfect understanding of the difficulties involved, so that stimulus may be given to younger men to evolve newer methods of treatment. A completely pessimistic attitude, which encourages only a biopsy and discourages any surgical attempt to remove the tumor, is not, in my opinion, the proper surgical policy. Certainly, there are areas in the brain resection of which produces a vegetative person. The surgeon's duty is to restore the patient to his former physical condition so far as is possible. This requires surgical judgment and surgical conscience. The problem of the surgical treatment of the glioblastoma cannot be answered by refusing to use the surgical methods at one's present disposal.

**Effect of *d*-Tubocurarine Chloride in Oil on Spasms Due to Disease of the Spinal Cord.** Dr. Benjamin Boshes and Dr. Herman Blustein.

Eight patients with lesions of the spinal cord and severe spasms were treated with *d*-tubocurarine chloride in oil. In no case were the spasms relieved, and in 4 cases they were increased. Toxic symptoms of blurred vision, double vision, nausea, vomiting, involuntary movements of the bowel, syncope, dyspnea and cyanosis appeared. These symptoms are believed to be of central origin. *D*-tubocurarine releases its central toxic effect before it produces a lissive or peripheral curare-like action; hence, it is of no value in the severe spasms incident to transverse lesions of the cord.

DISCUSSION

Dr. Alex J. Arieff: After Schlesinger's enthusiastic report on curare, I thought I would try it at Cook County Hospital not only for the condition reported on here, but for relief of spastic paraplegia, multiple sclerosis, postencephalitic parkinsonism and some hyperkinesias. The method was to inject purified chondodendron tomentosum extract (intocostrin®) to see how much relief would be obtained with an acute aqueous dose; if there was any effect, I tried a slower effect with *d*-tubocurarine chloride in wax, because the acute affect is valueless in treatment of any of the conditions mentioned.

Of 7 cases of multiple sclerosis and spastic paraplegia in which 60 to 100 units of intocostrin® was given, there was slight decrease in spasticity, which lasted for a very short time, in 3; in 2 cases there developed the side effects described here, which in 1 case were alarming for a short time. In a patient given 350 units of *d*-tubocurarine chloride the results were negligible; I was discouraged and felt that one was not warranted in giving larger doses. Of 2 cases of parkinsonism, there was no change in 1; in the other there were no side effects and the patient said she felt better, but there were no objective signs of improvement. In a case of Huntington's chorea 100 units gave a toxic effect without any change in the chorea. In a case of spastic paraplegia, with a daily dose of 80 units of introcostrin®, the patient felt best on the third day.

My results, therefore, were rather discouraging. A few patients asked for injections, but therapy with no side effects or objective relief is only psychotherapy, and to use curare for this is dangerous.

Dr. Paul C. Bucy: I should like to know how the dosage used in this study compares with that used by Dr. Schlesinger. Two points in this presentation confuse me. I do not understand what is meant by involuntary bowel movements in a patient with complete interruption of the spinal cord, and I should also like to hear a fuller explanation of what is meant by the complete recovery except for muscular spasms in case 8. It is my understanding that these patients had complete, or nearly complete, transection of the spinal cord. Such a result would be truly remarkable.

DR. HERMAN BLUSTEIN: In answer to Dr. Bucy's question about case 8: The patient is almost completely recovered. There is recovery of voluntary function of the muscles of the lower extremities, with only flexor spasms and bilaterally dislocated hips as a result of these spasms. We used more curare than Dr. Schlesinger did.

DR. BENJAMIN BOSHES: There is no simple way of explaining the action of curare. Curare is not a standard drug. Any sample one obtains is a mixture of many curares, and one would have to know the geographic origin of the drug to know what it will do. The curarines act entirely differently from the curares. When one speaks of the curare action, one means paralysis of the peripheral musculature. Actually, curare has three different effects: First, it has a lissive effect, a lessening of tone, so that a limb which had good tone becomes completely relaxed. Extensive studies have been made, and the consensus is that lissiveness is not a peripheral, but a central, action. Another effect is on the central and autonomic nervous systems. The curare acts in a toxic manner long before the peripheral action is evident; so if a curarine is injected, early central action should be expected. It is not strange, therefore, that one has failure when using *d*-tubocurarine in oil. The third, best known, action of curare is peripheral paralysis. One cannot predict what curare will do in a given case. A drug is discovered, then forgotten; someone rediscovers it, and there is both use and abuse; finally, the pendulum swings back to rational utilization of the substance. At present curare is being "overused."

**Eric Oldberg, M.D., *President, in the Chair***
***Regular Meeting, Oct. 12, 1948***

**Pheochromocytoma with Cerebral Hemorrhage: Psychoneurotic Implications.** DR. LEROY H. SLOAN and DR. ROBERT SCHLESINGER (by invitation).

A white man aged 23 was admitted to the Illinois Central Hospital as a patient of Dr. Clyde Landis on March 23, 1948. On the previous day he had sudden onset of severe headache, whereupon he shouted and screamed for help; he was seen by his physician and spent the day in bed. The following morning he felt much improved, but about 9:00 p. m. he again complained bitterly of headache, was very restless, thrashed about the bed, was at times disoriented and had a premonition of impending death. Suddenly right hemiplegia developed. On examination by his physician, his blood pressure was 180 systolic, and the urine showed a heavy deposit of albumin, without sugar or other elements.

On admission to the hospital, he was very noisy; his skin was cold and clammy; he perspired profusely; his temperature was normal, and he had pronounced tachycardia. The following morning his blood pressure was 218 systolic and 130 diastolic, the pulse rate 140 and the temperature 100 F. On examination he was extremely restless and presented all the signs of complete hemiplegia, hemianesthesia and hemianalgesia on the right side. Right homonymous hemianopsia was evident on routine flash tests and gross field determinations. There was ptosis of the left eyelid; both pupils were widely dilated but reacted to light; the fundi were normal; there was complete dissociation of ocular movements. A strong pilomotor reaction was present over the right arm. Sphincteric control was involuntary. The patient kept his head thrashing from side to side, made feeble attempts to carry out orders, seemed to recognize his parents, screamed unintelligible shouts and had occasional attacks of vomiting, associated with spastic contraction of the right arm.

The urine showed no albumin, sugar or pathologic elements. The Kahn reaction of the blood was negative. The spinal fluid was clear; the Wassermann reaction was negative; the colloidal gold curve was flat, and the fluid was under an initial pressure of 240 mm. of water. The blood sugar was 208 mg. and the urea nitrogen 27 mg., per hundred cubic centimeters. The patient died that night, with a rectal temperature of 110 F.

Autopsy, performed by Dr. J. B. Fuller, of the University of Chicago, revealed a retroperitoneal tumor, 6 cm. in diameter, overlying the right kidney; a few atheromatous plaques in the descending aorta, near the bifurcation of the iliac arteries; an adolescent type of thymus, and hyalinization of the afferent renal arterioles. The right adrenal gland weighed 8.82 Gm., and the left, 8.4 Gm. The brain showed a subarachnoid hemorrhage over most of the cortex of the left hemisphere and softening of the corresponding motor and sensory cortical areas. Examination of the brain after fixation revealed a massive cortical and subcortical hemorrhage of the left hemisphere with extension into the subarachnoid space.

Further inquiry into the history disclosed the occurrence of very severe headaches about one month before his death, which he had described as of exactly the type he suffered in the Army. They came suddenly and ended suddenly, lasting from thirty to sixty minutes; he would then feel well, although occasionally he was unable to sleep or sit and would pace the floor. These headaches occurred with increasing frequency.

During childhood he had had temper tantrums and periods of sudden onset of depression; these lasted from one-half to one hour and ended suddenly. After induction into the Army, he was reclassified for radio work because of nervousness. He left the United States in March 1944 and was transferred to the Philippines in December. On the boat he was suddenly seized with a severe panic reaction, became tremulous, noisy and restless and required sedation by packs and medication. His classification at various times was "hebephrenia, catatonia, mixed type of dementia precox," and he was separated from the service with the diagnosis of schizophrenia, simple type, with partial remission—a diagnosis which he resented deeply, insisting that he had softening of the brain. At home he became supersensitive, withdrew from social contacts and had sudden outbursts of temper, followed by equally sudden recovery.

Practically all the patient's difficulties could be traced to secretion of the large pheochromocytoma, which on sudden occasion poured out a large amount of epinephrine into the blood stream. The confusion of a so-called functional state of psychic origin with the symptoms due directly to a large pheochromocytoma recalls the equally confusing picture of a so-called functional epileptic state, now known to be due to hyperinsulinism.

The authors stated the opinion that the findings in this patient should be made part of his Army record.

DISCUSSION

DR. PAUL C. BUCY: Do you believe that this man's mental aberration, dating back five years, was the result of the tumor? How do you explain it, and in what way do you think the tumor gave rise to the symptoms?

DR. LEROY H. SLOAN: I believe it was because of the sudden flooding of the blood stream with a large amount of epinephrine, which can produce practically all the symptoms of which this man complained. Under even mild stress of exercise a great deal is thrown out; and under the stress and strain of Army life, as well as the tension of a return to a confused and misunderstood civilian existence, this amount would be greatly increased.

**Regeneration of Bone Following Relief of Pressure from Expanding Intracranial and Intraspinal Lesions.** DR. PAUL C. BUCY, DR. ROBERT F. HEIMBURGER (by invitation) and DR. JOEL F. SAMMET (by invitation).

Five patients with erosion of bone due to the persistent pressure of expanding soft tissues were followed by roentgenograms from one to thirteen years after the pressure had been relieved. In 2 of the patients the erosion was intracranial. The first, a woman aged 43, showed regeneration of the dorsum sellae one year after removal of an acoustic neurinoma. In the second, a girl aged 8 years, deep convolutional markings on the inner table of the skull disappeared, and the margins of the sella turcica regenerated one year after opening of the third ventricle had relieved the intracranial hypertension due to block of the aqueduct of Sylvius. The other 3 patients presented erosion of the medial surfaces of the vertebral pedicles due to expanding lesions within the spinal canal. In each of these patients, whose ages ranged from 3 to 20 years, the eroded vertebral pedicles regenerated and resumed their normal contour and position after removal of the intraspinal lesion. The pedicles not only regenerated but became more densely calcified than the adjacent normal pedicles. This increased density remained evident in the 3 patients throughout a period of observation of at least ten years. It was concluded from these cases that erosion of bone is a reversible process, occurring to a pronounced degree in children, but evident also in adults. Regeneration of eroded bone can be used as a criterion of the success of a procedure to relieve chronic pressure.

DISCUSSION

DR. REUBEN M. STRONG: One does not expect bone to regenerate significantly, except at sites of fracture. However, it is known that when new strains are put on bone there may be changes in shape and volume. In a case described by Roux (1892) a false joint developed as a consequence of imperfect union of the fragments of a fractured tibia. This was followed by extensive hypertrophy of the fibula, which became larger than the tibia and took over the functions of both bones. I suggest that the term "ossification" would be better than "calcification."

DR. PAUL C. BUCY: This, of course, is the situation which Dr. Oldberg pointed out a year or two ago, and which we are now able to confirm. I thank Dr. Strong for his discussion. One is obviously dealing with ossification, not calcification. It is surprising not only that calcium salts were replaced, but that this process has gone on beyond the normal, so that the pedicles are now much heavier than usual. Moreover, the pedicles which were pushed beyond the vertebral bodies have returned to a normal position and shape.

**Morphology of the Pial Blood Vessels and Its Bearing on the Formation and Absorption of Cerebrospinal Fluid.** DR. GEORGE B. HASSIN.

The pial arteries and veins, including the smallest ones, contain, in addition to the classic three tunics, an additional adventitia, which may be classified as periadventitia. This may be traced to the pia or the arachnoid, and in some instances it is represented by mesothelial cell nuclei. If the "endothelial" cover cell layer of Key and Retzius is to be considered a separate tunic enveloping, according to these authors, the adventitia (or rather the periadventitia), it should be conceded that a pial blood vessel possesses five tunics. Of these, the most constant and striking are the adventitia, the periadventitia and the "endothelial" layer of Key and Retzius. As it is not possible to demonstrate the presence of capillaries in the pia mater or the choroid plexus, one cannot speak of capillary periadventitia. The presence of the latter would render invalid the teaching of Mestrezat that the formation and

absorption of the cerebrospinal fluid are products of filtration of the plasma serum through the walls of the blood vessels, since the serum would have to pass through several powerful tunics. The anatomic, as well as the pathologic, facts, however, demonstrate clearly that the cerebrospinal fluid represents the tissue fluids of the brain, that it is absorbed by the perineurial spaces of the cranial nerves and the spinal nerve roots and that the choroid plexus extracts noxious substances (lipids, blood pigment, parasites) from the ventricular contents, to render them more absorbable.

DISCUSSION

DR. REUBEN M. STRONG: In experimental work done in my department which involved roentgen irradiation of pregnant rats, an offspring had hydrocephalus with enormous dilatation of the lateral ventricles. There was hyperplasia of the ependyma lining the cerebral aqueduct, resulting in blockage of the lumen. How can this occurrence be explained if the choroid plexus absorbs the cerebrospinal fluid?

DR. JOSEPH LUHAN: Dr. Hassin explained how tissue fluid can find its way into the subarachnoid spaces because there are continuous spaces. He stated that the tissue fluid flows directly into the ventricle. There is not an open route into the ventricle; there is the ependymal lining, which I assume is a barrier.

DR. VICTOR E. GONDA: Cushing demonstrated, I believe, that during intraventricular operations on the brain the choroid plexuses can be made dry on their surfaces by touching them with cotton and, after a short period, one can see the cerebrospinal fluid oozing from these surfaces, thus proving that the plexuses have something to do with secretion of the cerebrospinal fluid.

DR. JOHN MARTIN: Can Dr. Hassin explain the fact that in cases of congenital hydrocephalus, if the child survives operation, the hydrocephalus is often arrested after removal of the choroid plexus?

DR. PAUL JORDAN: I am not clear whether Dr. Hassin believes that tissue fluids are reabsorbed or that only the waste products are absorbed.

DR. GEORGE B. HASSIN: When the cerebral ventricles are obstructed, their contents cannot escape, regardless of the cause of the obstruction. It is not the retained fluid that is absorbed by the choroid plexus, but its waste products, such as lipids or blood pigments, which are picked up from the fluid by the tuft cells. The fluid itself is absorbed by the perineurial spaces (of the cerebral nerves and the spinal roots), which are continuous with the subdural and subarachnoid spaces of the brain and the spinal cord. This statement also answers Dr. Jordan's question.

There is a communication between the ventricles and the cerebral parenchyma. Wislocki and Putnam demonstrated the existence of such a connection experimentally (*Am. J. Anat.* **29**:313, 1921).

"Sweating" of the arachnoid was emphasized by Spina, before Cushing, in cases of experimentally increased peripheral blood pressure. This phenomenon does not speak for or against the choroid plexus's being the source of the cerebrospinal fluid. It is hard, however, to understand how brain tissue can be kept dry, in view of the fact that it contains 70 per cent fluid and only 30 per cent solids. Were it not for the enormous amount of capillaries and blood vessels, the brain would be practically a liquid mass.

I know of no instance of cure of hydrocephalus by any therapeutic or surgical method recommended. Putnam claimed reduction in the size of the head amounting to several inches after plexectomy. I studied some of the brains on which he operated and found nothing that would speak in favor of such a procedure. Is this operation (plexectomy) popular?

**Eric Oldberg, M.D., *President, in the Chair***
***Regular Meeting, Dec. 14, 1948***

The scientific program was presented by members of the faculty of the State University of Iowa College of Medicine, Iowa City.

**Hypothalamic Factors in Animal Behavior.** DR. W. R. INGRAM, DR. M. D. WHEATLEY, DR J. R. KNOTT and MR. W. R. MCCRUM, Iowa City.

Hypothalamic lesions of rather specific type are associated with a number of behavior changes in cats, including savageness. Since such lesions presumably alter certain circuits related to the cerebral cortex, attempts were made to determine possible physiologic changes in cortical function by use of the electroencephalogram. Such experiments necessitated numerous control observations. It was found that $\beta$-erythroidine hydrobromide in the doses used did not alter the cat's electroencephalogram. The effects of various oxygen and carbon dioxide mixtures were studied in connection with the type of artificial respiration used. A large series of experiments with normal and savage cats failed to reveal any significant differences with the animals under curarization when the electroencephalograms were recorded through the scalp. In a few experiments, however, chronic implanted electrodes were used and records obtained from nondrugged, unrestrained animals, under both undisturbing and disturbing conditions. There were indications that the electroencephalograms of savage cats do not conform to normal patterns in these circumstances.

It is well known that morphine produces violent excitement in cats. This is accompanied with intense hyperthermia. Hypothalamic lesions which involve temperature control mechanisms prevent this hyperthermia and diminish the excitement.

**Periarteritis Nodosa: Its Clinical Diagnosis and Etiology.** DR. C. H. MILLIKAN, Iowa City.

It has been assumed that the diagnosis of periarteritis nodosa can be made only by biopsy, and the disease is commonly discovered only at autopsy. A series of cases presented a similarity in general complaints and physical signs, as well as other manifestations limited to a particular system of the body. The criteria for clinical diagnosis were discussed. Lesions were shown which explained the appearance of certain signs seen in cases of periarteritis nodosa.

The various concepts of the etiology of periarteritis nodosa were briefly reviewed, including the conclusion reached by Rich and his associates that an unusual sensitivity to a foreign substance is the cause of the disorder. The result of an attempt to reproduce Rich's experiments was reported. This attempt, and additional variations of Rich's original work, produced none of the lesions of periarteritis. It was concluded that the evidence for the "sensitivity theory" is inadequate and that further investigation of the subject should be made.

DISCUSSION

DR. F. HILLER: I should like to ask Dr. Millikan whether he thinks that this condition is a disease entity. Anatomically, the similarity of, for instance, syphilitic cerebral endarteritis (Heubner's endarteritis) and the acute infectious forms of panarteritis is obvious. There seem to exist variations, that is, the

temporal, or cranial II type of arteritis, in which the disease is self limited with respect to localization and time. I should like to know Dr. Millikan's opinion concerning the place which, in his experience, temporal arteritis has in the general syndrome of periarteritis nodosa.

DR. VICTOR E. GONDA: What is the average time of survival after diagnosis is made? How many of the 17 patients mentioned by Dr. Millikan are alive? I ask this question because not long ago almost all diagnoses were made post mortem.

DR. ALEX J. ARIEFF: I should like to know the incidence which the 17 cases represent. My associates and I do not see these cases often, and I am sure we must have missed a number at the Cook County Hospital and in other services.

DR. C. H. MILLIKAN, Iowa City: I agree with what Dr. Hiller has said. I am not sure that arteritis is a primary disease. The lesions are associated often with rheumatic fever or with disseminated lupus erythematosus. We have simply been trying to follow up any leads that present themselves. Periarteritis nodosa may have few systemic manifestations. Whether it is the same as temporal arteritis I am not sure.

Seven of the patients are still alive after three years. I think it is possible that the disease does not carry the mortality that has been generally supposed. Cases occur, for the most part, in the neurologic service.

**Intracranial Aneurysms and Polycystic Kidney.** DR. A. L. SAHS, Iowa City.

During the course of investigation of approximately 150 cases of intracranial aneurysm, 60 of which were verified at autopsy, 4 instances of associated congenital polycystic kidney were found. The respective ages of the patients were 24, 28, 42 and 26. Hypertension was present in each instance. In the first case the aneurysm was situated at the junction of the left internal carotid and the middle cerebral artery; in the second case, on the right anterior cerebral artery at its junction with the anterior communicating artery, and in the third, at the first bifurcation of the right middle cerebral artery. In the fourth case, aneurysms were situated at six bifurcations over the anterior portion of the circle of Willis. An aneurysm of the left internal carotid artery provided the source of the subarachnoid hemorrhage.

All six of the aneurysms in the fourth case, as well as bifurcations from other sites, were subjected to extensive histologic study. Serial sections were made from material embedded in pyroxylin, and the sections were stained for elastic tissue and with Masson's trichrome stain. The development of the aneurysms was discussed, with the aid of lantern slides.

DISCUSSION

DR. OSCAR SUGAR: Is there any direct connection between aneurysms and polycystic kidney? We have had a large number of patients with aneurysms at the Psychopathic Institute, none of whom has had any disease of the urinary tract that I know of.

DR. VICTOR E. GONDA: Was the polycystic kidney bilateral?

DR. A. L. SAHS, Iowa City: The incidence of 4 in 60 proved cases and in 95 suspected cases is considerably higher than the incidence of polycystic kidney in the general population. I tried to substantiate the assumption that these cases were probably congenital or developmental in origin; the incidence is higher than that encountered in general practice. The polycystic kidneys were bilateral.

**Calcified Subdural Hematoma of an Estimated Thirty Years' Duration.**

Dr. Donald B. Sweeney and Dr. Jess T. Schwidde, Iowa City.

A white man aged 39 was admitted with the chief complaint of attacks of numbness and weakness of the left upper extremity for the previous eighteen months. Such attacks occurred approximately every two weeks, their duration varying from a few minutes to many hours. On occasion the right upper extremity was simultaneously involved, in which case dysphasia was also experienced. The parents asserted that the patient had "always had a large head." There was no history of head injury.

The general physical and neurologic examinations disclosed no remarkable features except for a maximum head circumference of 64.5 cm. Roentgenograms demonstrated an "extremely large skull with numerous punctate and curvilinear areas of density throughout the left cerebral hemisphere." Ventriculograms disclosed a decided shift of the ventricular system to the right. A craniotomy in the left temporoparietal region revealed a large, yellowish subdural mass, which was not adherent to the dura. Approximately 50 cc. of yellowish, grumous material was aspirated. The mass itself covered the anterior two thirds of the cerebral hemisphere, and its greatest thickness was approximately 3.5 cm. It extended from the superior longitudinal sinus, above, to the mesial reaches of the temporal fossa, below.

Microscopic examination of the aspirated material revealed no cholesterol crystals. Its cholesterol content, as determined by chemical assay, was 422 mg. per hundred cubic centimeters, of which 314 mg. consisted of cholesterol esters. Total solids amounted to 6.8 per cent and total fats to 0.88 per cent (by weight).

Histologic study of the walls of the cyst revealed hyalinized fibrin; fibrous and fibroblastic lamellations, enclosing old blood pigment, and scattered flecks of calcium. The grumous material from the cystic cavity was described as an "acellular, homogeneous mass." Trepanation of the right temporal vault failed to disclose a lesion comparable to that encountered on the left.

Convalescence was well established when the patient was discharged to his home, on the fortieth postoperative day. There is inferential evidence to support the belief that the patient had harbored a subdural lesion for more than thirty years.

DISCUSSION

Dr. Milton Tinsley: My colleagues and I observed a similar calcified hematoma in an 11 year old girl. Her history indicated a cerebral hemorrhage at birth. There was a bulging fontanel, but no operative procedure was carried out. At present she has right hemiplegia, right homonymous hemianopsia and generalized convulsive seizures. Plain roentgenograms of the skull revealed a calcified lesion in the left parietal region. A pneumoencephalogram revealed a porencephalic cyst on the left and a calcified hematoma, the latter being apparently subdural. The ventricle was pulled up toward the lesion. In view of her normal intelligence and her adjustment to her environment and the fact that medication controlled her seizures, surgical intervention was not contemplated at this time.

Dr. Eric Oldberg: A definite point of diagnosis in Dr. Tinsley's case was that the calcified lesion appeared separated from the skull and the ventricles were pulled toward the hematoma, instead of being pushed away, as in the case shown this evening.

Dr. Walter R. Kirschbaum: A calcified subdural hematoma is always a long-standing condition and has its origin in disturbance of the vascular supply

of the dura during infancy. It is not a direct consequence of mere trauma to the skull and to the dura, with bleeding of a torn vessel. In any such event, the trauma is likely to produce later fibrous organization and membranes, which may enclose hygromatous cysts. However, the real pachymeningitis hemorrhagica interna is due either to a primary vascular proliferation of the subdural endothelial tissue, the vessels of which may later calcify, or to an inflammatory vascular reaction. Both possibilities, the result of birth trauma, avitaminosis, infection or marasmus, lead to exudation and organization of larger or smaller hemorrhages. Anoxemia of the proliferated vascularized subdural endothelial membrane produces calcification. Traumatic subdural (or surgical) hematoma and pachymeningitis hemorrhagica interna may lead to common end stages; but they are distinct disease entities, the causes of which are as yet not fully understood.

**Physiology of Sleep: Wave Characteristics and Temporal Relations of Human Electroencephalograms Simultaneously Recorded from the Thalamus, the Corpus Striatum and the Surface of the Scalp.** Dr. John R. Knott, Iowa City; Dr. Robert Hayne, Des Moines, and Dr. H. Russell Meyers, Iowa City.

Electrical potentials derived from (*a*) multiple electrodes in the corpus striatum and its neighboring structures; (*b*) surface electroencephalographic electrodes in the standard positions on the scalp, and/or (*c*) multiple electrodes in the thalamus were simultaneously recorded in 8 human subjects at the onset, during and at the offset of sleep. The records derived from 2 subjects in whom sleep occurred "spontaneously" were not essentially different from those of subjects in whom sleep was induced by seconal sodium® (sodium 5-allyl-5-[methylbutylbarbiturate]). The position of the deeply placed electrodes was ascertained after each experiment by means of pneumoencephalography and previously established tridimensional coordinates of the human brain.

The wave characteristics of the sleep potentials were evaluated in view of the recordings obtained from 12 control subjects. Three types of wave frequencies regularly appeared, in the order indicated: fast waves (18 to 24 per second), random (delta waves, 3 to 4 per second) and spindles (12 to 15 per second). The earliest changes were detected almost simultaneously in the thalamus and in the corpus striatum; comparable cortical changes lagged behind by four to nine minutes. During the offset of sleep, the wave changes receded in reverse order, and a residue of fast waves was demonstrated in the deep nuclei several minutes after the cortical potentials had returned to normal and the patient had awakened.

DISCUSSION

Dr. F. A. Gibbs: The paper we have just heard is additional evidence in support of the conclusion that during sleep the thalamus and the deeper centers drive the electrical activity of the cortex. Mirison and his co-workers have shown that bursts of 8 to 12 per second during sleep induced by pentobarbital sodium come from the region of the internal medullary lamina of the thalamus. In a recent study of vascular accidents, Dr. Cress and my wife have found that the absence of 14 per second activity is a reliable lateralizing sign, indicating a subcortical lesion which prevents the deep centers from driving the overlying cortex. Since in sleep there is an apparent thalamization of cortical activity, sleep provides a condition in which thalamic disorder is projected into an area where it can be easily recorded, namely, on the outer convexity of the hemispheres.

As the authors have stated, they have not found the point of origin of sleep potentials, but they have demonstrated that they arise in deep structures. Their future reports will be watched with interest, for it is likely that further research along these lines will elucidate the neurophysiology of sleep—a subject on which we are strangely ignorant.

DR. VICTOR E. GONDA: At present it is not believed that there is in the brain a circumscribed area that can be designated a "sleep center." It is most likely that the whole brain participates in the function called sleep. Although many pathologic specimens, examined after a condition resembling sleep during some types of encephalitic processes, have shown that the brunt of the damage was in the region of the basal ganglia, this fact alone does not prove that that area is the "center" of sleep. Can the authors in any way deduce from their investigations that the area they examined has anything to do with sleep?

DR. RUSSELL MEYERS, Iowa City: I am afraid our studies have shed no light on the question raised. We have taken simultaneous records from three areas—the thalamus, the corpus striatum and the scalp. The earliest changes evidently appear simultaneously in the thalamus and in the corpus striatum, or changes in the corpus striatum occur within a few moments of changes in the thalamus. It does not appear, therefore, that the corpus striatum "drives" the thalamus or vice versa. It seems more likely that both are driven by a still more fundamental focus of activity, which, as sleep deepens, somewhat later dominates the cerebral cortex. Thus far we have not tapped in on this hypothetic focus of electric activity with our electrodes. We intend to explore systematically for it with the stereotaxic instrument recently exhibited, at the Seventy-Fourth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 14-16, 1948.

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## NEW YORK NEUROLOGICAL SOCIETY AND THE NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

**Lewis D. Stevenson, M.D., *President, New York Neurological Society, in the Chair***

***Combined Meeting, Nov. 9, 1948***

**Presidential Address.** DR. LEWIS D. STEVENSON.

**Neural Metabolism in Relation to Function.** DR. RALPH WALDO GERARD, Chicago (by invitation).

Metabolism makes function possible by supplying energy or substance. Different links in the chain of reactions have different importance. The functional weight of a given step can be explored by combined metabolic and physiologic studies, especially with the aid of inhibitors to block specific reactions. A high degree of specificity is, however, less common than could be wished.

Experiments with the inhibitor of oxidative processes, such as methyl fluoroacetate, and with inhibitors of cholinesterase, such as di-isopropyl fluorophosphate and tetraethyl pyrophosphate, in brain and nerve show many parallelisms in their action on function and respiration and in protection against their activity. These agents act on other enzyme systems than cholinesterase.

Although glucose is the main fuel of the brain, it does not supply the activity in neural metabolism. Glutamic acid and glutamine change with and influence the functional state of the nervous system. Experiments also point to changes in

phospholipin with nerve activity and in nucleoprotein with material movement along axons. It is also possible to influence separately the resting and active metabolism of nerve, further evidence of their qualitative difference.

Quantitative and qualitative differences in metabolism also appear throughout the central nervous system, and these are related to the effects of hypoxemia, hypoglycemia and many diseases. In fact, most neurologic disease has a metabolic basis.

**Combined Lateral and Ventral Pyramidotomy in Treatment of Paralysis Agitans.** DR. JUDAH EBIN (by invitation).

This paper was published in the July 1949 issue of the ARCHIVES, page 27.

DISCUSSION

DR. E. JEFFERSON BROWDER: If it were not so late, I should like to discuss in detail some of the problems which have presented themselves to me in the light of Dr. Ebin's study. The best I can do is to express my view of what is being done at present. Dr. Ebin has added another surgical procedure for the modification of the tremor and rigidity of paralysis agitans. From the technical standpoint, this makes seven operations: Bucy's cortical resection, Klemme's cortical ablation, Wyke's cortical section, my capsular operation, Meyers' pallidofugal section, Putnam's dorsolateral section in the upper cervical region and, now, Dr. Ebin's operation. I have had personal experience with four of these operations, but have not used the operation carried out by Bucy, that proposed by Wyke or the modification of Putnam's operation that Dr. Ebin has presented this evening.

The Bucy operation leaves the patient with a useless upper extremity and a spastic lower extremity; in other words, one exchanges tremor for paralysis, and I cannot believe that this is a bargain. The excision of area 4 leaves the hand virtually useless. Moreover, in some of the patients operated on by Bucy there were recurrent convulsive seizures subsequent to this operation. Therefore it seems to me this is not an operation which is generally applicable in cases of paralysis agitans.

Up to the present I have examined 9 patients, each of whom had excision of a part or all of the premotor cortex. One of these 9 patients was operated on by Meyers, when he was associated with me before the war; 1, by myself, and the remaining 7, by Klemme. All of them had postoperative spastic hemiplegia; in addition, 7 of the 9 had recurring convulsions. From all accounts, Dr. Klemme has performed his operation on several hundred patients, and one cannot believe that those whom I have examined are fair representatives of the results that he has been able to obtain in the majority of his patients. It is well known, however, that recurring convulsive seizures are not an infrequent sequel to any operation that interferes with normal premotor function. Because of this frequent complication following resection of the premotor cortex, one should have great hesitancy in offering the operation as a procedure of choice for paralysis agitans.

The best results that I have seen from any procedure have been those following the pallidofugal section of Meyers. I have never performed this myself but have had the opportunity to follow the patients on whom he operated when he was still with me. There were too many undesirable side effects, or at least I thought so at the time, for this operation to be offered as a routine procedure for relief of paralysis agitans. Last spring at the annual meeting of the American Neurological meeting in Atlantic City, Meyers reported that up to that time he had operated on 11 additional patients at the University of Iowa Hospital, where he is now

located. Very satisfactory results had been obtained, and no enduring side effects had been reported. He had eliminated some of the undesirable features of the operation.

I have reported previously the results that have followed section of the anterior limb of the internal capsule (Parkinsonism: Is It a Surgical Problem?, *New York State J. Med.*, **47**:23, 1947; Section of the Fibers of the Anterior Limb of the Internal Capsule in Parkinsonism, *Am. J. Surg.* **75**:1, 1948; End Results Following the Capsular Operation for Parkinsonism, *S. Clin. North America*, April, 1948, p. 390). Suffice it to say that one can abolish the tremor and lessen the rigidity by sectioning about three fourths of the fibers coursing in the anterior capsule. The section is carried out to the point where there is striking paresis of the hand at the time of operation; subsequent thereto the patient can carry on in a fairly normal manner. One cannot perform this operation bilaterally, as one can the operation reported by Dr. Ebin. It is to be hoped that Dr. Ebin's operation will make it possible to carry out bilateral sections at one sitting.

My personal experience with the Putnam operation in 3 cases has been that the tremor and rigidity may be abolished for a period, but that as soon as the motor power returns the tremor reappears. It seems, therefore, that the Putnam operation is also unacceptable as a means of control of the rigidity.

Dr. James C. White has reported on 2 patients on whom operation was carried out at the Massachusetts General Hospital under the direction of Dr. Wyke. One was a patient with pronounced rigidity and minimal tremor. The brain, when exposed, was found to be atrophic and covered with a milky pia-arachnoid. Some difficulty was encountered in identifying area 4 s. No changes in either tremor or rigidity followed the operation, namely, section through the cortex between area 4 s and 6. The second patient was a better subject. She, too, had severe rigidity and minimal tremor. After a section designed to cut the fibers connecting areas 4 s and area 6, there was considerable improvement in the component of rigidity. This improvement was about equal on the two sides, an observation casting doubt on the effect of the cortical section itself.

I hope that time and further experience will show that Dr. Ebin's operation on the upper cervical portion of the spinal cord will be an effective measure in the control of the tremor and rigidity of paralysis agitans.

# Book Reviews

**Lehrbuch der Nervenkrankheiten in 30 Vorlesungen.** By Robert Bing. Eighth Edition. Price, 52 Swiss francs. Pp. 743, with 230 illustrations. Benno Schwabe & Company, Klosterberg 27, Basel, Switzerland, 1947.

I have learned a great deal from this great work, which I have read, nay studied assiduously, in detail and in its entirety. The author, who on May 8, 1948 attained three score years and ten, has put into his book the results of his enormous clinical experience during a lifetime of practice. With this profound experience, he has integrated his knowledge of the international neurologic literature. His command of this literature—the old, new and newest—is awe inspiring. Because much of the foreign literature is not easily accessible, Bing's critical analysis of it is the more valuable. While he gives due consideration to laboratory and technical methods, the book is essentially a textbook of clinical neurology—the neurology of Babinski and Oppenheim. Bing conjures up before the eyes of his readers the vanishing art of diagnosis in neurology by the simplest methods: with one's eyes and ears and the use of a hammer, pin and ophthalmoscope. The book is highly didactic; the presentation is well rounded; the continuity is logical. Bing is extremely cautious and exercises the highest degree of self-critique; he does not attempt to impose his own views on the reader; he talks *with* his reader, but never *to* him. The chapters on therapy are particularly valuable, since they offer detailed, "ready for use" information based on extensive experience in practice, and not on bookish knowledge.

Despite the fact that Bing avails himself of little or no secretarial help—or perhaps because of it—the book is very carefully edited and the number of inaccuracies and misprints is negligible. Everything in the book is amazingly well ordered and correct.

Some criticism might be offered on the following minor items:

The "Notalgia paresthetica" of Astwazaturow (page 65) may involve not only the area of the lumbar nerve but also that of the thoracic.

It seems doubtful whether in myotonia the muscles of the upper extremities are "in most cases less affected than the lower" (page 140).

It is not quite correct to call the Mendel-Bechterew, Rossolimo, Weingrow, Trömner and Hoffmann reflexes "pathologic" (pages 171-172). They are only pathologic exaggerations of basically normal reflexes, a fact that should be stressed from a practical, as well as from a physiologic and a didactic, standpoint. I cannot subscribe to Bing's emphatic statement: "It is a fact of greatest importance that functional increase of reflexes is never—but never—(*nie und nimmer,* page 631) accompanied with . . . the Mendel-Bechterew phenomenon." Elsewhere I (The Examination of Reflexes: A Simplification, Chicago, The Year Book Publishers, Inc., 1945, p. 168) have pointed out that a positive Mendel-Bechterew phenomenon cannot in itself be regarded as a definite sign of a pyramidal lesion. Not only does the physiology of this reflex make it evident but also clinical experience shows that the reflex is found in normal persons. Nistri (*Riv. di pat. Nerv.* **69**:168, 1948) recently found this reflex present in 21.5 per cent of normal persons under 40 years of age and in 13.8 per cent of those beyond this age.

Speaking of pathologic associated movements in the spastic paretic muscles (page 172), Bing, having mentioned the thumb sign of Wartenberg and the tibialis sign of Strümpell, mentions also the radial phenomenon, which "consists of compulsory dorsification of the hand on volar flexion of the fingers." This is a normal phenomenon.

In the acute apoplectic form of bulbar paralysis, Bing (page 181) includes also thrombosis of the inferior posterior cerebellar artery (Wallenberg's syndrome). He says that the course of this paralysis is "in most cases fatal." I am inclined to believe that the opposite is true, and to agree with Nielsen (A Textbook of Clinical Neurology, ed. 2, New York, Paul B. Hoeber, Inc., 1946, p. 152) that the course in Wallenberg's syndrome is "relatively benign." It is, in my experience, even strikingly so.

When Bing speaks of changes in the optic nerve in multiple sclerosis (page 208), he says that the disturbances of vision thus produced "occasionally disappear, even completely." "Occasionally" is certainly an understatement.

On page 246 it is stated that the reflexes of defense in pyramidal lesions "represent skin reflexes." The term "skin reflexes" hardly covers their nature, since such reflexes can be elicited not only by stimulation of the skin but by active and passive movement as well.

The heterolateral associated movement in hemiplegia (page 381) cannot be regarded as "analogous with dissociation of the facial innervation in hemiplegia." The physiologic mechanism of the two is different.

Of the phenomena seen in hemiplegia (page 385), Bing has this to say: ". . . platysma phenomenon (*signe du peaucier*) is called the energetic contraction of the platysma on the healthy side which becomes manifest when the patient with cerebral hemiplegia opens his mouth."

When Babinski (*Bull. et mém. Soc. méd. d. hôp. de Paris.* **14**:1104 [July 30] 1897) first presented a case with this sign, and described it in seven lines, he spoke of "associated spasm of the platysma of the healthy side in organic hemiplegia." It is interesting to note that Monrad-Krohn (The Clinical Examination of the Nervous System, ed. 8, New York, Paul B. Hoeber, Inc., 1947, p. 119) regards this sign as an associated movement which "may be abolished in pyramidal lesions." However, the normal contraction of the platysma muscle is not an associated movement. It is, so to speak, an auxiliary movement, since the platysma participates in the opening of the mouth, especially on wide and forceful opening. The essential of this phenomenon is this very lack of participation of the platysma on the hemiplegic side. This is plainly due to weakness of the muscle on the affected side, but not to "spasmodic contraction" on the healthy side. Babinski (*Gaz. d. hôp.* **73**:521, 533, 1900) himself, in a later article, refuted his first view of this phenomenon as an associated spasm and explained it not as a spasm on the healthy side, but as an expression of weakness on the paretic side. He mentioned that the same phenomenon can occur in peripheral facial paralysis. Babinski said: "I think, in effect, that it is not a spasm of the normal side, but, rather, it is a paresis of the platysma on the affected side." This, doubtless, is the correct interpretation of this phenomenon.

For a new edition, the following suggestions are timidly offered: The newer-accepted nomenclature should be used—femoral nerve instead of crural (page 8 and others); semispinalis muscle instead of complexus (page 107); serratus anterior muscle (page 154) instead of anticus; trapezius instead of cucullaris (page 154). It would be advisable to name the reflexes according to the muscles involved; brachioradial reflex is, for instance, better than radius reflex. It is not a reflex of the radius, but one of the brachioradial muscle. In this way, such physiologically inadequate terms as "costal margin reflex" (page 15), "symphysis pubis reflex" (page 15), "flexor tendon reflex" (page 15), "spinal adductoric reflex" (page 16), "fibular reflex" (page 16) would be avoided. It is also hoped that a new edition will not employ such terms as "tendon and bone reflexes" (pages 15, 206, 631) and "genuine tendon reflex" (page 16) and will not call the reflex of Mayer and Léri "genuine joint reflexes." These terms are not adequate either from a physiologic or a didactic standpoint. It is also hoped that the term

"abdominal reflex" will not be used, that a sharp distinction will be made between the abdominal muscle reflex and the abdominal skin reflexes and that the clinical meaning of their dissociation will be stressed. It will also be appreciated by every reader if the author will somewhat dampen his ardor for words with Greek roots. Certainly no one will miss such terms as *Xerosalgie* (page 59); *Gampsodaktylie* (page 625); *Dysnystaxis, Dyskoimesis* and *Dysphylaxia* (page 628); *Haphalgesie* (page 667); *Chasma, Ptarmus,* and *Rhenchospasmus* (page 671). A welcome change would be the elimination of footnotes. A textbook reads more smoothly without them, and it is better to incorporate them in the text.

The whole neurologic world would owe a great debt of gratitude to Professor Bing if he would undertake to give references for every author he mentions, as did Kinnier Wilson. But the hope that such a herculean task will be attempted is, I fear, just a hope.

ROBERT WARTENBERG, M.D.

**Diagnostic Signs, Reflexes, and Syndromes.** By William Egbert Robertson, M. D., and Harold F. Robertson, M. D. Third edition. Price $4.50. Pp. 376. F. A. Davis Company, 1914-16 Cherry St., Philadelphia, 1947.

The purpose of this book, now in its third edition, is to standardize diagnostic signs, reflexes and syndromes. The junior author is medical chief to the neuropsychiatric department of a general hospital of high repute. The authors state in the preface that such men as W. G. Spiller, Charles H. Frazier and N. W. Winkelman "furnished valuable source information." All this lured me to browse in the sections devoted to neurologic terms. Here are some of the things I have learned. They are all amusing or startling, or even frightening. (The italics are mine.)

"Piotrowski's sign: Percussion of the tibialis anticus muscle induces *dorsal flexion* and supination of the foot" (pages 14 and 62). Piotrowski himself said that dorsiflexion and supination of the foot on the elicitation of his reflex are seen in normal persons, and are inconstant and of no pathologic significance. The essential characteristic of Piotrowski's reflex is *plantar* flexion, not dorsiflexion, of the foot.

"Bechterew #3. Plantar reflex seen in pyramidal tract disease. A tap on the dorsum of the foot with a percussion hammer induces plantar flexion of the *foot*" (page 39; similar definition on pages 257 and 274). The reflex of Bechterew consists of flexion of the *toes,* not the foot.

"Wernicke's hemiopic sign: . . . An isolated lesion in the *cimeus* may cause a lateral hemiopia . . ." (page 68). Is "cimeus" a new term, or should it be "chiasm"?

"Ciliospinal reflex: This implies a response on the part of the ciliary body and spinal cord, the reflex consisting of dilation of the pupil when the *vein of the neck* is irritated or stimulated" (page 71). It could not possibly be "vein of the neck"!

"Combined plantar sign: The simultaneous disappearance of the cortical and spinal plantar reflex met with in hysteria" (page 75; similar definition on page 158). This sign is apparently what is called "mute sole." Though L. Alexander (Pullen's Medical Diagnosis, p. 803) thinks, too, that this may occur in hysteria, the statement in this form is untenable, since the "mute sole" may indicate a pyramidal lesion (Kino, F.: Zur klinischen Bedeutung des fehlenden Fussohlenreflexes ["Stumme Sohle"], Klin. Wchnschr. **6**:1280, 1927).

"Cushing's angle tumor syndrome. Cerebellopontine tumor. . . . As a late manifestation, cerebellar phenomena . . . and the tendency *to fall to the opposite side* . . ." (page 84). Falling to the opposite side in the case of a unilateral cerebellar lesion?

"Eye closure reflex: A percussion tap over the *supraorbital nerve* results in contraction of the orbicularis palpebrarum with consequent closure of the lids" (page 108). This reflex, the orbicularis oculi reflex, is not contingent on the tapping of the nerve but is a plain, simple muscle stretch reflex.

"Hemiplegia. Triceps reflex: *In this condition,* the so-called triceps tendon or elbow reflex may be elicited" (page 144). It is but a normal reflex.

"Rossolimo's reflex or sign: Occurs in lesions of the pyramidal tract as in organic hemiplegia. When the great toe of the paralyzed side is lightly percussed or stroked upon its plantar surface, *extension* or adduction of the toe results. (Authors' Note—This may be regarded as a *variant of Babinski's #2*)" (page 145; similar definition on pages 274 and 289). This statement contains three grave errors: 1. Rossolimo's reflex, as described by Rossolimo in 1908, is elicited by percussing not the great toe, but the smaller toes. Rossolimo himself emphasized (1902) that movement of the great toe on tapping has no pathologic significance. 2. In Rossolimo's reflex, plantar flexion of the toe takes place, not extension of the toe, as in the Babinski reflex. 3. The Rossolimo sign is a muscle stretch reflex; the Babinski sign is part of the flexor withdrawal reflex, a manifestation of so-called medullary automatism. It is completely erroneous and highly confusing to regard Rossolimo's reflex as a *variant* of Babinski's. The Oppenheim, Chaddock, Schaefer, Gordon and other reflexes can be regarded as variants of the Babinski reflex, but by no means the Rossolimo reflex.

"Holme's [misprint, should be Holmes'] rebound sign: Known also as the rebound phenomenon. This occurs in the unilateral disease of the cerebellum. The patient flexes the arm on the side *opposite* to the lesion, resistance to this flexion being made by the examiner . . ." (page 150). *Opposite* to the lesion? The rebound sign is elicited on the side of the lesion.

"Hypothenar reflex: As the name implies, this is a reflex manifested in the hypothenar area when pressure is made upon the pisiform bone" (page 157). And what happens when the reflex is positive?

"Stewart-Holmes sign: . . . but in hypotonia, flexion of the arm persists without participation of the *biceps*" (page 158). This presumably should read "triceps."

"Insanity, ulnar sign: Consists of analgesia in the area of the ulnar nerve on one side. Frequently present in the mentally diseased, excluding general paresis" (page 160). This, to put it mildly, is horrifying, hair-raising, revolting nonsense! It brings cold sweat to the brow of every thinking neurologist and psychiatrist! It is a mystery how such a thing could be printed in a book appearing anno Domini 1947.

"Jaw jerk reflex: This is quite *similar to Chvostek's sign,* although a more pronounced phenomenon" (page 165). The jaw reflex is a stretch reflex involving the masticatory muscles. Chvostek's sign, on the other hand, is due to mechanical irritation of the facial nerve with a resultant contraction of the facial musculature. Where is the similarity?

"Klumpke-Déjerine syndrome: This is *essentially a combination* of Klumpke's lower arm palsy and Déjerine's radiculitis or root zone syndrome" (page 171). This statement would adorn a book on "Humor in Neurology," which ought to be written. The literature contains no description of a combined Klumpke lower arm palsy and Déjerine radiculitis syndrome. Klumpke's lower arm palsy is often called Klumpke-Déjerine or Déjerine-Klumpke palsy. The real "combination" was that Miss Augusta Klumpke, a young lady from San Francisco (1859-1927), went to study in Paris. While she was a final year student, she married, in 1890, the famous neurologist J. Déjerine. Further confirmation of this fact could have been given by Professor Hardy, who gave the bride away, and by Professor Landouzy, "the second witness" at the wedding.

"Knee jerk reflex: This is sometimes spoken of as Westphal's sign, the patella reflex, or the quadriceps reflex" (page 172). No! Westphal's sign does not mean the *presence* of a knee reflex, but its *absence!* Why "jerk" *and* "reflex"?

Korsakoff's syndrome (page 173) is described as a "psychosis with a polyneuritis, disorientation, muttering delirium, insomnia, illusions and hallucinations," but the cardinal syndrome, loss of memory for recent events with confabulation, is not mentioned!

"Mendel's reflex: . . . The reflex results from percussing the dorsum of the foot. Under normal conditions, dorsal flexion of the second to the fifth toes occurs. In *cerebellar* tract disease, plantar flexion of the toes results" (page 203). On page 62 it is said: "Cerebellar tract disease: For differentiation from the normal reflex which results from percussion of the dorsum of the foot, see Mendel's reflex." Mendel's reflex has nothing to do with a cerebellar lesion.

On page 225 one reads: "Nonne's cerebellar agenesis syndrome: Same as Cestan's syndrome, which see." Of this, one could say anything from "not accurate" to "pure nonsense." In 1891, Nonne first described a clinical syndrome caused by cerebellar atrophy. Pierre Marie, in 1893, on the basis of this work of Nonne and that of others, established the syndrome of hereditary cerebellar ataxia. In a later work (1905), Nonne approved of this term as very suitable. In Germany, Pierre Marie's ataxia is sometimes called "Nonne-Marie disease." This Nonne syndrome has nothing, plainly nothing, to do with the Cestan or Cestan-Chenais syndrome, which is correctly described on page 64. The latter has to do with a circumscribed bulbar lesion. Cestan and Chenais, in their original description, in 1903, called their syndrome "hemiplegia of Avellis' type associated with the ocular sympathetic syndrome."

This is a reference book. Therefore, names and terms should be deadly accurate! Unfortunately, this is not the case. The inaccuracies are too many to mention. Here are only a few: It should be Quinquaud, not Quinquad (pages 9, 276); Revue neurologique, not Review Neurology (page 31); Schaefer, not Schaffer (page 35); Gaussel, not Granseel or Ganssel (pages 75, 143, 146); pavor nocturnus, not pavor nocturnas (page 82); astereognosis, not asteriognosis (page 89); Avellis', not Avelli's (pages 89, 297); Souques', not Souque's (pages 112, 130, 306); Bruns', not Brun's (pages 52, 114); Ganser, not Gauser (page 123); Guillain, not Guilland (pages 135, 203); Gowers', not Gower's (pages 144, 188); Strümpell, not Strumpel (page 145); Kinnier, not Kinnear (pages 153, 271); Nielsen, not Nielson (page 224); Riddoch, not Riddock (page 284); Winkelman, not Winkleman (page 371), and so on.

Hughlings Jackson (page 194), Marcus Gunn (page 198) and Argyll Robertson (page 292) should not be hyphenated, but Raymond-Cestan (page 263) should. The syndrome carrying the last name was described (1902), not by "Raymond Cestan," but by Fulgence Raymond and Raymond Cestan. The correct name for this syndrome is, therefore, the Raymond-Cestan syndrome.

There is no "Mr. Andre Barre of the Urologic Clinic of the Salpêtrière" (page 38). There is a psychiatrist in Paris by the name of André Barbé, and there was a neurologist in Paris by the name of Jean Alexandre Barré, a pupil of Babinski, now in Strasbourg.

Warren Tay and Bernard Sachs were not, as is mentioned four times (pages 9, 67, 159 and 334), "New York neurologists." Only Sachs was, whereas Warren Tay was a London ophthalmologist.

This chaff has been gleaned from the neurologic wheat—I wonder how much chaff can be found in other fields. It is a great pity that the authors do not appear to realize how grave and weighty is their responsibility when they offer this reference book as an informative source. As the book stands, a fourth edition—unless carefully revised and edited—should never see the light of this world.

ROBERT WARTENBERG, M. D.

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